Differential Patterns of Cognitive Decline in Anterior and Posterior White Matter Hyperintensity Progression

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Background and Purpose—White matter hyperintensities (WMHs) found on brain MRI in elderly individuals are largely thought to be due to microvascular disease, and its progression has been associated with cognitive decline. The present study sought to determine patterns of cognitive decline associated with anterior and posterior WMH progression.

Methods—Subjects included 110 normal controls, aged ≥60 years, who were participants in the Duke Neurocognitive Outcomes of Depression in the Elderly study. All subjects had comprehensive cognitive evaluations and MRI scans at baseline and after 2 years. Cognitive composites were created in 5 domains: complex processing speed, working memory, general memory, visual-constructional skills, and language. Change in cognition was calculated using standard regression-based models accounting for variables known to impact serial testing. A semiautomated segmentation method was used to measure WMH extent in anterior and posterior brain regions. Hierarchical multiple linear regression models were used to evaluate which of the 5 measured cognitive domains was most strongly associated with regional (anterior and posterior) and total WMH progression after adjusting for demographics (age, sex, and education).

Results—Decline in complex processing speed was independently associated with both anterior ($r^2=0.06$, $P=0.02$) and total WMH progression ($r^2=0.05$, $P=0.04$). In contrast, decline in visual-constructional skills was uniquely associated with posterior progression ($r^2=0.05$, $P<0.05$).

Conclusions—Distinct cognitive profiles are associated with anterior and posterior WMH progression among normal elders. These differing profiles need to be considered when evaluating the cognitive correlates of WMHs. (Stroke. 2010;41:00-00.)

Key Words: cognition ■ neuropsychology ■ white matter disease

Cerebral white matter areas that appear hyperintense on T2-weighted MRI are frequently found on MRI scans of elderly individuals. Although the pathophysiological causes of white matter hyperintensities (WMHs, also called “white matter lesions”) are varied, in elders they are generally considered to be a marker of small vessel disease. A small number of large-scale longitudinal studies have shown an association between cognitive decline and WMH progression in nondemented older adults. Although declines in processing speed are often associated with WMH progression, impairments in memory or other cognitive skills have also been implicated. Thus, the relation between WMHs and the domains of cognitive decline remains uncertain.

One investigative approach has been to explore the differential relationship between cognition and periventricular compared with deep WMHs. The method of measurement of WMHs varies among studies, and the appropriateness of this anatomic dichotomization remains controversial. Not surprisingly, results have been inconsistent across studies with some finding progression of periventricular WMHs and others progression of deep WMHs to be more strongly associated with cognitive decline.

Regional progression of WMHs may differ with the frontal lesions progressing most and occipital lesions least. The impact of anterior WMHs on cognitive decline is also greater than that of posterior lesions in patients with vascular cognitive impairment. Furthermore, a cross-sectional diffusion tensor imaging study of 52 healthy participants aged 19 to 81 years found that white matter degradation in regions of interest in anterior brain areas was related to reduced processing speed and working memory, whereas decline in posterior regions was associated with decreased inhibition and task switching. Taken together, these findings suggest that the distinction between anterior and posterior white

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matter might provide additional characterization of the relationship between cognition and WMHs. The primary purpose of the study was to examine the cognitive correlates of anterior and posterior WMH progression.

Methods

Participants

Participants (n=110) were community-dwelling older adults who served as controls for the Duke University Medical Center Neurocognitive Outcomes of Depression in the Elderly (NCODE) study. The study was approved by the Duke Institutional Review Board and all participants provided informed consent. Subjects were between 60 and 83 years of age at baseline and had at least a high school education (see Table 1 for further demographic data). Other eligibility criteria included nonfocal neurological examination, no history of depression based on the Diagnostic Interview Schedule portion of the Duke Depression Evaluation Schedule, and no self-report of neurological or depressive illness. Participants selected for the present study underwent baseline and 2-year follow-up brain MRI scan and neuropsychological evaluations.

Materials and Procedure

Demographic and Health Data

Demographic data were recorded at baseline. Subjects also completed a questionnaire at baseline and 2-year follow-up to assess the presence or absence of several medical conditions, including hypertension, diabetes, heart problems, and stroke.

MRI Protocol

Participants completed MRI scans at baseline and after approximately 2 years. Subjects were imaged with a 1.5-T whole-body MRI system (Signa; GE Medical Systems, Milwaukee, Wis). A rapid sagittal localizer scan was acquired for alignment, and a dual-echo fast spin-echo acquisition was obtained in the axial plane for morphometry. Axial images had 3-mm thickness without interslice gaps. Images were processed in Duke’s Neuropsychiatric Imaging Research Laboratory on SunOS workstations. Volume measurements were performed with a Neuropsychiatric Imaging Research Laboratory-modified version of MrX software (General Electric Corporate Research and Development, Schenectady, NY). The segmentation protocol, or process for converting image intensity to segmented tissue types, has been described previously. Briefly, it is a semiautomated method that uses the multiple MR contrasts available to identify different tissue classifications through a “seeding” process, in which a trained analyst manually selects pixels in each tissue type to be identified (gray matter, white matter, cerebrospinal fluid, gray and white matter lesions, or background). Infratentorial lesions were not included. WMH volumes were obtained in periventricular and deep white matter. Infarcts, which were present on some follow-up scans, were not included with these lesions. Cerebrum volume was defined as the sum of gray and white matter and lesions.

Additional procedures were required to obtain measures of WMH and cerebrum volume of the cerebrum in anterior and posterior brain areas (Figure) and have been described previously. First, an axial plane was created along the anterior-posterior commissural line, dividing superior regions from inferior. Next coronal planes were created perpendicular to the axial plane at the anterior and posterior extent of the corpus callosum. Finally, a third coronal plane was created at the midpoint between the first 2 coronal planes, which divided the brain into anterior and posterior halves. The middle coronal plane was used to separate anterior and posterior brain regions for white matter lesion volumes. WMH progression was calculated by subtracting WMH volume at baseline from WMH volume at the follow-up for each participant. This calculation was performed for WMHs in anterior and posterior halves of the brain as well as overall WMHs. Similar computations were used to measure cerebrum volume change over time.

Neuropsychological Testing

Cognitive data were obtained from the neuropsychological testing date closest to MRI acquisition (days between MRI and testing: at baseline mean=4.44, SD=21.37; at follow-up mean=2.96, SD=19.92). The test battery was comprised of the Consortium to Establish a Registry in Alzheimer’s Disease neuropsychological battery and supplemental cognitive tests. The Consortium to Establish a Registry in Alzheimer’s Disease measures included (1) the Mini Mental State Examination; (2) language tasks consisting of category fluency (Animal Naming) and object naming (15-item Boston Naming Test); (3) visual constructional praxis and visual memory, requiring copy of 4 geometric designs, delayed recall, and delayed recognition procedures; and (4) verbal learning and memory consisting of immediate recall of 3 learning trials of a 10-item word list, delayed recall, and recognition of target words from nontarget foils. Additional measures included the Logical Memory subtest of the Wechsler Memory Scale–Revised, the Benton Visual Retention Test, the Controlled Oral Word Association Test from the Multilingual Aphasia Examination, the Trail Making Test, Symbol Digit Modalities Test, Digit Span subtest of the Wechsler Adult Intelligence Scale–Revised, and a separate Ascending Digit Span task modeled after the Digit Ordering Test.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>2-Year Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>70.65 (5.55)</td>
<td>...</td>
</tr>
<tr>
<td>Education, years</td>
<td>15.98 (2.31)</td>
<td>...</td>
</tr>
<tr>
<td>Female</td>
<td>80 (72.7)</td>
<td>...</td>
</tr>
<tr>
<td>Race</td>
<td>White 97 (88.2)</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>Black 9 (8.2)</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>Mixed 4 (3.6)</td>
<td>...</td>
</tr>
<tr>
<td>MMSE*</td>
<td>28.85 (1.32)</td>
<td>28.55 (1.56)</td>
</tr>
<tr>
<td>Hypertension†</td>
<td>24 (21.8)</td>
<td>28 (25.4)‡</td>
</tr>
<tr>
<td>Diabetes†</td>
<td>4 (3.6)</td>
<td>4 (3.6)‡</td>
</tr>
<tr>
<td>Heart problem†</td>
<td>8 (7.3)</td>
<td>13 (11.8)‡</td>
</tr>
<tr>
<td>Stroke†</td>
<td>0 (0)</td>
<td>2 (1.8)§</td>
</tr>
</tbody>
</table>

*Mean (SD). †No. (%). ‡Two missing cases. §Three missing cases. MMSE indicates Mini Mental State Examination.
Individual raw test scores were transformed into z scores using the observed difference score was calculated on all tests using the following formula:

\[ z = \frac{x - \mu}{\sigma} \]

where \( z \) is the sample mean for a given test, and \( SD \) is the sample SD on that same test. Next, the individual z scores for the be standardized, \( M \) is the sample mean for a given test, and \( SD \) is the sample SD on that same test. Next, the individual z scores for the tests comprising each composite were averaged to compute standardized scores for each composite.

Standardized regression based models were used to quantify cognitive progression. Specifically, linear regression of the difference scores on the initial scores was used to generate a formula for predicting a difference score from any baseline score for each test. Using this formula, the deviation from expected change was calculated for each participant on each test. Standardized z difference scores were calculated on all tests using the following formula:

\[ z = z_{predicted} - z_{observed} \]

where \( z_{predicted} \) is the predicted difference score from the regression equation for a given subject. Composite difference scores were computed by calculating the average z difference score for tests comprising each composite.

### Statistical Analysis

Given prior findings showing more prominent anterior than posterior WMH progression, we evaluated regional WMH load at baseline by computing independent sample t tests on WMH volumes in anterior versus posterior regions at baseline. Paired sample t tests on WMH volumes at baseline and follow-up were conducted to determine whether lesions had progressed. To determine whether rate of progression of WMHs varied by region, changes in regional lesion volumes were calculated by subtracting individual values at baseline from follow-up scores in anterior and posterior regions with a 2-sample t test on these difference scores.

To determine which cognitive domain(s) would be most strongly associated with total and regional WMH progression, 3 hierarchical multiple linear regressions (P < 0.05 to enter and P > 0.10 to remove) were calculated, 1 on each WMH progression score (ie, total, anterior, and posterior). Age, education, and sex were entered in the first step of these models to adjust for their effect. Next, cognitive composite difference scores were entered stepwise as predictors. This approach might have underestimated the independent contribution of individual cognitive domains due to shared variance among cognitive composites; however, it allowed the identification of the cognitive domains that were most impacted by regional WMH progression at the same time as avoiding overestimation of associations between cognition and WMH based on common variance with other domains. Similar analyses were performed on WMH load and cognitive composite scores at baseline to evaluate the relation between these variables. For those models not meeting regression assumptions, models were rerun using data converted into ranks to assess the robustness of the findings.

The sample size provided an approximate 80% power to detect, for any particular predictor, an increase in the model \( R^2 \) of 0.04 corresponding to a moderate effect size. SPSS for Windows (Version 12; SPSS Inc) was used for all analyses.

### Results

#### Regional WMH Progression

Table 3 shows descriptive statistics on WMH volumes (in milliliters) at baseline and follow-up (mean follow-up interval was 737.49 days, SD = 26.21 days). Mean volumes did not significantly differ in anterior and posterior lesions on baseline scans (P = 0.06). WMHs progressed in both anterior and posterior regions (Table 3), but there was no difference in progression by region (P = 0.40).

#### Relationship Between Cognition and Regional WMH Load at Baseline

Hierarchical multiple regressions of WMH load at baseline showed that age was associated with total (P < 0.01), anterior (P < 0.01), and posterior (P = 0.02) WMH load. Although initial analyses showed that general memory was associated with anterior (F = 4.56, P < 0.01, \( R^2 = 0.18 \)) and total (F = 3.26, P = 0.02, \( R^2 = 0.13 \)) WMH load after controlling for demographics, secondary analysis using ranked data did not find an independent relationship.

### Cognitive Correlates of Regional WMH Progression

Results from hierarchical multiple regression analyses indicated that change in complex processing speed was uniquely associated with anterior WMH progression, whereas change in visual-constructional skills was solely associated with posterior WMH progression (Table 4) after adjusting for demographics. Demographic variables did not predict regional or total WMH progression (all Ps > 0.20), but note that our sample had a restricted age range. The results were similar when the analyses were repeated with data transformed into ranks and after adjusting for change in cerebrum volumes.

### Discussion

In the present longitudinal study, we investigated the relationship between regional WMH progression (anterior versus posterior) and decline in cognition (ie, complex processing speed, working memory, general memory, language, and visual-constructional skills) in a sample of community-dwelling elderly individuals without a history of stroke or dementia. We found that decline in complex processing speed was the most important
cognitive correlate of anterior WMH progression, whereas decline in visual-constructional skills was the most important correlate of posterior WMH progression. These results are consistent with previous studies showing an association between WMH progression and cognitive decline\(^2\)–\(^6\) but extend these findings by showing a differential pattern of cognitive decline related to anterior and posterior WMH progression among normal elders. Consistent with other large-scale longitudinal studies, decline in complex processing speed was independently associated with both overall and anterior WMH progression.\(^7\)–\(^9\) The only study of this kind that assessed processing speed and did not find an association was the Austrian Stroke Prevention Study. In that study, nonspeeded attentional/working memory tasks were included along with speeded tasks as part of an attention/ speed composite metric, possibly explaining the difference.\(^3\)

We also found that that decline in visual-constructional skills was uniquely associated with posterior WMH progression. The Austrian Stroke Prevention Study\(^7\) also reported an association between WMH changes and visual-motor skills as measured by the Purdue Pegboard. However, this is a speeded motor task substantially different from the nonspeeded visual-constructional tasks included in our study. Furthermore, neither of the other large-scale studies with repeated MRI and cognitive testing nor the 1 diffusion tensor imaging study exploring anterior versus posterior white matter integrity assessed this cognitive domain.\(^10\) Visual constructional skills, as measured by the Block Design subtest of the Wechsler Adult Intelligence Scale, have been found to be associated with WMH in patients with stroke\(^27\) and healthy elders,\(^28\) and our finding linking it to changes in posterior brain areas is consistent with established knowledge on functional neuroanatomy.\(^29\) Harmonization standards identified visuospatial skills as 1 of 4 domains to be assessed by the 60-minute neuropsychological test protocol.\(^30\) Results from validation studies of this protocol will offer more data regarding the significance of visual–spatial deficits in posterior vascular brain changes.

Because both total and anterior WMH progression were associated with the same cognitive composite (ie, complex processing speed), but posterior WMH progression was associated with visual-constructional skills, anterior WMH progression best reflects the effects of total WMH progression on cognition. One possible explanation for this finding is that anterior WMH progression places a greater burden on cognition than posterior WMH progression, which is consistent with findings on patients with vascular cognitive impairment.\(^9\)

Whether the loss of brain volume that is associated with progression of lesion load might account for the relationship between WMH load and cognition has been controversial. In the Austrian Stroke Prevention Study,\(^7\) the relationship between WMH and cognition was lost when brain atrophy was included in the same model. In our study, however, the relationship between WMH and cognition remained even when change in cerebrum volume was included. This is consistent with other studies\(^4\)–\(^5\) and suggests that brain atrophy is not a mediator of the relationship between WMH progression and cognitive decline.

Cognitive variables were not predictive of WMH load at baseline after adjusting for demographics suggesting that certain variables can have differing effects on baseline versus longitudinal performance.\(^31\) Longitudinal studies may be more sensitive in identifying the relationship between cognition and WMH, in part because demographic variables may influence the change association less than they do the baseline relationships.

Our study has several strengths. It used repeated MRI scanning and comprehensive cognitive testing to explore anterior versus posterior WMH progression and its association with cognitive decline. WMH load and cognition were assessed using valid and sensitive measures. WMH load was assessed using a semiautomated method with proven reliability.\(^11\) A comprehensive neuropsychological testing battery allowed evaluation of cognitive domains using composite measures, which tend to be more robust and valid than single test scores. Most longitudinal studies exploring the relationship between WMH and cognition use a single cognitive test and measure a limited number of cognitive domains, typically those domains that have been found by early studies to be related to WMHs, possibly resulting in oversight of subtle effects of WMHs on other cognitive domains. Additionally, the present study used standard regression-based models to assess cognitive change. This approach controls for variables known to impact serial cognitive testing such as regression to the mean and practice effects, which are of critical importance to consider in any longitudinal study of cognition.\(^25\) This methodology is a more precise measure of cognitive change than the subtractions of raw or standardized scores and also offers the advantage of yielding difference scores that are on a standardized scale across tests and domains, allowing for meaningful comparisons on the degree of change across measures despite their having different raw score scales.

The study also has several limitations. The subjects were relatively healthier than the general population, and thus, the findings may not be applicable to all community-dwelling
elders. The sample size permitted the detection of only a moderate effect; a study with a larger number of subjects is required to identify more subtle differences. Replication of these findings in other populations with known risk factors and documented cerebrovascular disease would help support the generalizability of the results. Although our method of quantifying WMH was reliable, the cause and pathological correlates of WMHs as identified are unknown as is the etiology of concomitant WMHs and atrophy. Therefore, additional work is needed to determine the clinical significance of the findings.

The results of this longitudinal study in nondemented older adults suggests differential patterns of cognitive decline associated with regional (anterior versus posterior) WMH variation. The findings may have implications in choosing a neurocognitive marker for the evaluation of regional WMH and exploring the effects of candidate therapies.

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Disclosures
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References
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