Association of White Matter Hyperintensity Volume With Decreased Cognitive Functioning

*The Framingham Heart Study*

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**Objective:** To examine the relationship between white matter hyperintensity (WMH) volume on magnetic resonance images and cognitive tests in a large, population-based sample.

**Methods:** Quantitative magnetic resonance imaging and neuropsychological evaluations were performed in 1820 dementia- and stroke-free participants from the Framingham Offspring Cohort. The WMH volume relative to total cranial volume was computed; WMH volumes more than 1 SD above the age-predicted mean were defined as large. Adjusting for age, sex, education, height, and Framingham Stroke Risk Profile, we examined the relationship between WMH and 3 cognitive factors derived from a neuropsychological test battery (verbal memory, visuospatial memory and organization, and visual scanning and motor speed) and 3 individual measures of new learning, abstract reasoning, and naming.

**Results:** Compared with those with no or little WMH volume, participants with large WMH volume performed worse on the cognitive factors of visuospatial memory and organization (*P* = .04) and visual scanning and motor speed (*P* = .01), as well as on new learning (*P* = .04), but not on verbal memory (*P* = .52).

**Conclusions:** In this younger community-based population of nondemented individuals, those with large WMH volume, as compared with those with less or no WMH volumes, performed significantly worse in cognitive domains generally associated with frontal lobe systems and, to a lesser extent, the medial temporal area. Further study will clarify whether large WMH volume and associated cognitive impairment lead to future risk of stroke or dementia.

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Imaging research finds that white matter hyperintensities (WMHs) occur in individuals presumed free of neurologic disease, as well as those with stroke and dementia. The cause of WMH, however, remains a matter of debate; it may be associated with ischemic disease, as supported by positive associations with cerebrovascular risk factors, or represent a variety of processes including normal aging, cerebrovascular disease, and Alzheimer disease.

Although the cause of WMH remains unclear, accumulating evidence suggests that the clinical manifestations result in poorer performance in executive functioning, particularly among subjects who were not demented. Generally, limited sample sizes as well as subject sampling bias attenuate the significance of these findings.

In the population-based Cache County study of nondemented, mild cognitive impairment, Alzheimer disease, and neuropsychiatric groups, Bigler et al found a significant relationship between WMH and cognitive performance but were unable to draw conclusions because of heterogeneity in the data. In the Rotterdam Scan Study, de Groot et al reported that psychomotor speed was more strongly associated with WMH than was memory. Inferences of their findings to the general population, however, may be limited by the absence of definitive measures of executive function and use of a semiquantitative measure of WMH rather than a quantitative measure.

Each of these population-based studies was restricted to the study of older individuals, limiting our understanding of the full impact of WMH in earlier life. Data from the Atherosclerosis Risk in Communities study suggest that WMH may be a consequence of cerebrovascular risk factors that manifest at an early age.

Thus, although the prevalence and potential cognitive consequences of WMH are well documented, previous research has major methodologic limitations, such as insufficient sample size, different magnetic resonance (MR) imaging measuring techniques, and biased subject sampling, in-
Table 1. Neuropsychological Test Battery

<table>
<thead>
<tr>
<th>Cognitive Factors</th>
<th>Major Cognitive Domains Assessed</th>
<th>Measures of Performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>WMS Logical Memory, paragraph A</td>
<td>Factor 1: Verbal Memory</td>
<td>Immediate recall, delayed recall, delayed recognition</td>
</tr>
<tr>
<td>WMS Visual Reproductions</td>
<td>Visual memory</td>
<td>Immediate recall, delayed recall, delayed recognition</td>
</tr>
<tr>
<td>Hooper Visual Organization</td>
<td>Visual perception</td>
<td>Total score</td>
</tr>
<tr>
<td>Trails A and B*</td>
<td>Factor 2: Visuospatial Memory and Organization</td>
<td>Time to completion (minutes) for each test</td>
</tr>
<tr>
<td>Additional tests</td>
<td>WMS Paired–associate learning</td>
<td>New learning</td>
</tr>
<tr>
<td>WMS Paired–associate learning</td>
<td></td>
<td>Total score at immediate recall: (No. of hard pairs recalled + No. of easy pairs recalled)/2</td>
</tr>
<tr>
<td>WAIS Similarities (13 pairs)</td>
<td>Factor 3: Visual Scanning and Motor Speed</td>
<td>Immediate recall of hard items</td>
</tr>
<tr>
<td>Boston Naming Test* (30 items)</td>
<td>Abstract reasoning</td>
<td>Immediate recall of easy items</td>
</tr>
<tr>
<td>Wide Range Achievement Test–Reading 3*</td>
<td>Language, naming</td>
<td>Immediate recall of hard items</td>
</tr>
<tr>
<td></td>
<td>Reading, native intelligence</td>
<td>Total score</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total score without cues</td>
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<td></td>
<td>Total raw score</td>
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Abbreviations: WAIS, Wechsler Adult Intelligence Scale; WMS, Wechsler Memory Scale.
*Halstead Reitan Neuropsychological Test Battery.

including emphasis on the assessment of older individuals. The Framingham Offspring Study involves a community-based cohort whose ages span 6 decades and who have been longitudinally studied for cardiovascular risk and the development of clinical stroke and dementia for more than 30 years. This relatively young, large study population provides an unprecedented opportunity to detect subtle, but significant, relationships between WMH and cognitive performance associated with normal aging.

STUDY METHODS

The Framingham Offspring Cohort, recruited in 1971, has undergone 7 periodic physical and medical examinations to identify risk factors for cardiovascular and cerebrovascular disease.

We compared the demographic characteristics of members of the Offspring cohort who participated fully in the MR imaging study with those of (1) participants who underwent the NP portion but refused the MR imaging and (2) participants who declined the NP and MR imaging study altogether for any reason: illness, claustrophobia, contraindications, or refusal. Our analysis confirmed the well-documented sample bias that occurs with population-based MR imaging studies; MR imaging study participants were younger and healthier than nonparticipants. Although vascular risk factors were more common in nonparticipants, the direction of these findings suggests that any significant negative correlations between these risk factors and cognition are conservative estimates of the general population.

WMH MEASURE

DeCarli et al provided a detailed description of the quantification of WMH volume. We considered WMH volume as a continuous variable, but previous research from the Framingham Heart Study indicated that only large WMH volume (WMH-L) was linked to higher vascular risk, suggesting that only extensive changes in WMH have clinical significance among those with no neurologic disease. Thus, for these analyses, we used the same binary WMH variable used in the previous Framingham Heart Study, indicating no or little WMH volume (WMH-N) vs WMH-L (group definitions are presented in the “Results” section).

NP TEST BATTERY

The NP battery consisted of tests sufficient to provide a comprehensive cognitive profile, all administered according to standard protocols (Table 1).
STATISTICAL ANALYSIS

Age is a strong predictor of WMH volume. Hence, to remove the strong age effect from our analyses, we first grouped participants according to age group (35-44 years [n = 52], 45-54 years [n = 49], 55-64 years [n = 63], 65-74 years [n = 51], 75-84 years [n = 13], and ≥85 years [n = 2]); 1 participant younger than 35 years was excluded, bringing the analysis sample size to 1819. Second, participants were categorized as having large (WMH-L) or no or nonlarge (WMH-N) WMHs within each age group (adjusted for head size by dividing WMH by total cranial volume [TCV]) before the categorization) as follows. The natural log of the WMH/TCV ratio was linearly regressed vs age. A participant was categorized as having WMH-L when the residual (predicted WMH/TCV minus actual WMH/TCV) was greater than 1 SD of the mean residual for the participant’s age group. We based this categorization on the natural log of WMH/TCV as opposed to untransformed WMH/TCV because of the highly skewed distribution of the WMH/TCV ratio.

Previous factor analyses described elsewhere identified 3 cognitive domains: (1) verbal memory, (2) visuospatial memory and organization, and (3) visual scanning and motor speed (see Table 1 for tests composing each factor). We used the natural log of scores for Trails A and B, immediate recall, delayed recall, and delayed recognition to correct for skewed distribution. Additional cognitive measures of new learning, abstract reasoning, and naming were composed of scores from individual NP tests. Although the primary measure for new learning is immediate recall after the learning trials, we also included scores of delayed recall to assess retention of newly learned verbal stimuli. Also analyzed were the scores from the individual tests that composed the 3 cognitive factors.

We assessed the significance of the difference in NP measures (both cognitive factors and individual tests) between the WMH groups by means of analysis of covariance adjusting for sex, age, years of education, height, and the Framingham Stroke Risk Profile. This profile is a composite score of individual risk factors summarizing the 10-year probability of stroke.

RESULTS

There were no significant differences in the WMH groups for any demographic measure, risk factor score, or total brain volume (Table 2).

For the cognitive factor visuospatial memory and organization, participants with WMH-L volumes performed significantly worse than participants with WMH-N volumes (P = .04) (Table 3). Similarly, for the visual scanning and motor speed factor, WMH-L volumes were associated with poorer performance than WMH-N volumes (P = .01). For the verbal memory factor, performance did not differ between the 2 groups (P = .52). For individual tests of abstract reasoning and naming, no differences between the 2 groups were found (P = .47 and .33, respectively), whereas for new learning (immediate recall score), participants with WMH-L volumes did worse than participants with WMH-N volumes (P = .04).

For the significant visuospatial memory and organization factor, an analysis of the components showed that the Hooper Visual Organization total score was the only test result significantly different between WMH groups.
correlated with total WMH volume and WMH in other cerebrovascular disease risk factors, the presence of WMH is associated with increased prevalence of mild cognitive impairments that are likely to increase lifetime risk of Alzheimer disease or vascular dementia. Recent studies suggest that WMH-L volumes are associated with increased prevalence of mild cognitive impairment. Ongoing prospective studies will clarify whether WMH-L volume and the associated cognitive impairment indicate future risk of developing vascular dementia, Alzheimer disease, or other types of dementia. Given the potential for the treatment of cerebrovascular disease risk factors, the presence of WMH-L volumes may serve as a good measure of the need for more aggressive treatment.

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