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,[1,2] as well as those with stroke[3,4] and dementia.[5-7] 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,[8-12] or representative of nonspecific brain changes that reflect a variety of processes including normal aging, cerebrovascular disease, and Alzheimer disease.[13]

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.[14-17] Generally, limited sample sizes as well as subject sampling bias attenuate the significance of these findings.

In the population-based Cache County comparison study of nondemented, mild cognitive impairment, Alzheimer disease, and neuropsychiatric groups, Bigler et al[14] 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[18] 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[19,20] 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

Cognitive Factors	Major Cognitive Domains Assessed	Measures of Performance
	Factor 1: Verbal Memory	
WMS Logical Memory, paragraph A	Verbal memory	Immediate recall, delayed recall, delayed recognition
	Factor 2: Visuospatial Memory and Organization	
WMS Visual Reproductions	Visual memory	Immediate recall, delayed recall, delayed recognition
Hooper Visual Organization[4]	Visual perception	Total score
	Factor 3: Visual Scanning and Motor Speed	
Trails A and B*	Simple attention, concentration, mental flexibility/executive function	Time to completion (minutes) for each test
Additional tests		
WMS Paired–associate learning	New learning	Total score at immediate recall: (No. of hard pairs recalled + No. of easy pairs recalled)/2 Immediate recall of easy items Immediate recall of hard items Total score at delayed recall: No. of hard pairs + No. of easy pairs recalled Delayed recall of easy items Delayed recall of hard items
WAIS Similarities (13 pairs)	Abstract reasoning	Total score
Boston Naming Test[5] (30 items)	Language, naming	Total score without cues
Wide Range Achievement Test–Reading 3[6]	Reading, native intelligence	Total raw score

Abbreviations: WAIS, Wechsler Adult Intelligence Scale; WMS, Wechsler Memory Scale.
*Halstead Reitan Neuropsychological Test Battery.

cluding 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.

METHODS

STUDY PARTICIPANTS

The Framingham Offspring Cohort, recruited in 1971, has undergone 7 periodic physical and medical examinations to identify risk factors for cardiovascular and cerebrovascular diseases.[21] The initial Offspring cohort consisted of 5124 men and women; 88% of survivors (3539 of 4031) participated in Examination 7 in 1998 to 2001.

From 1999 to 2001, surviving members of the Offspring cohort were asked to take a neuropsychological (NP) test battery and to undergo brain MR imaging. The institutional review board at Boston University, Boston, Mass, approved the study protocol, and all participants provided informed consent. Of the 2187 participants who agreed to undergo NP testing, 1889 also had MR imaging. We eliminated 47 participants who had a clinical stroke (n=28) or diagnoses of probable dementia (n=2), multiple sclerosis (n=6), or other neurologic illnesses (n=11). A consensus review process determined whether a clinical stroke[22] or probable dementia[23] was present. An additional 22 participants had missing data. After all exclusions, total study size was 1820 (966 women, 854 men; age range, 34-88 years; mean±SD age, 61.1±9.40 years). We did not exclude potential cases of mild cognitive impairment because the intent of this study was to document the naturally occurring relationship between WMH and cognition within a nondemented sample. The MR imaging and NP testing were performed on the same day for 97.3% of participants and within 6 months for 99.5% of participants.

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[12,24,25]; 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[26] 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,[27] 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,[28] eg, 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**).

Table 2. Background and Risk Factor Characteristics

Characteristic	Subject Group* WMH-N (n = 1579)	WMH-L (n = 240)	*P* Value
Age, y	61.1 (9.4)	61.5 (9.4)	.49
Sex, % F	52.8	54.4	.66
FSRP score	0.08 (0.093)	0.09 (0.104)	.14
WRAT-Reading score	48.6 (5.2)	48.7 (4.7)	.57
MMSE total score	28.8 (1.4)	28.7 (1.6)	.16
Education, %			
<High school graduate	3.6	3.8	.67
High school graduate	32.2	34.7	
Some college or vocational college	25.8	23.0	
College graduate/postgraduate	38.4	38.5	
Total brain volume†	77.9 (3.1)	77.8 (3.6)	.65
WMH volume†	0.05 (0.04)	0.26 (0.27)	<.001
WMH volume log transformed‡	–3.34 (0.86)	–1.73 (0.81)	<.001

Abbreviations: FSRP, Framingham Stroke Risk Profile; MMSE, Mini-Mental State Examination; WMH-L, large white matter hyperintensities; WMH-N, no or nonlarge white matter hyperintensities; WRAT, Wide Range Achievement Test.

*Data are expressed as mean (SD) unless otherwise specified.

†Expressed as a percentage of total cranial volume.

‡Expressed as the natural logarithm of percentage of total cranial volume.

STATISTICAL ANALYSIS

Age is a strong predictor of WMH volume.[26] 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=449], 55-64 years [n=632], 65-74 years [n=531], 75-84 years [n=153], 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 grouping on the natural log of WMH/TCV as opposed to untransformed WMH/TCV because of the highly skewed distribution of the WMH/TCV ratio.[29]

Previous factor analyses described elsewhere[30] 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.[31,32]

Table 3. Results From Individual Test Measures

Neuropsychological Measure	Subject Group, Mean (SD)* WMH-N (n = 1579)	WMH-L (n = 240)	*P* Value†
Verbal memory			.52
LM-IR	11.38 (3.41)	11.42 (3.51)	.72
LM-DR	10.43 (3.66)	10.50 (3.40)	.66
LM-Rec	9.50 (1.23)	9.58 (1.16)	.32
VMO			**.04**
VR-IR	9.09 (3.20)	8.65 (3.20)	**.10**
VR-DR	8.22 (3.38)	7.84 (3.39)	.17
VR-Rec	3.08 (1.02)	3.00 (0.98)	.35
Hooper VOT	25.16 (3.11)	24.60 (3.32)	**.02**
VSM			**.01**
Trails A	32.96 (16.75)	34.49 (14.04)	**.07‡**
Trails B	84.36 (64.67)	98.79 (97.70)	**.004‡**
New learning			
PA-IR	13.89 (3.30)	13.43 (3.53)	**.04**
PA-IE	16.69 (1.45)	16.50 (1.69)	**.05**
PA-IH	5.33 (2.98)	5.00 (3.06)	**.09**
PA-DR	8.31 (1.47)	8.11 (1.56)	**.04**
PA-DE	5.88 (0.40)	5.87 (0.43)	.72
PA-DH	2.44 (1.29)	2.24 (1.39)	**.02**
Abstract reasoning			
Sim total	16.76 (3.62)	16.84 (3.28)	.47
Boston Naming Test	33.17 (2.85)	33.31 (2.34)	.33
WRAT	48.60 (5.17)	48.67 (4.66)	.57

Abbreviations: DE, delayed recall of easy items; DH, delayed recall of hard items; DR, delayed recall; IE, immediate recall of easy items; IH, immediate recall of hard items; IR, immediate recall; LM, Logical Memory; PA, paired associate; Rec, recognition; Sim, Wechsler Adult Intelligence Scale Similarities; VMO, visuospatial memory and organization; VOT, Visual Organization total score; VR, Visual Reproductions; VSM, visual scanning and motor speed; WMH-L, large white matter hyperintensity; WMH-N, no or nonlarge white matter hyperintensity; WRAT, Wide Range Achievement Test.

*Unadjusted mean performance scores.

†*P* values adjusted for age, sex, years of education, height, and Framingham Stroke Risk Profile. Boldface values indicate statistical or marginal significance.

‡Based on log-transformed data.

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

($P=.02$). Approaching significance was Visual Reproductions–immediate recall ($P=.10$). For the significant visual scanning and motor speed factor, Trails B was significantly different between groups ($P=.004$), while Trails A was of borderline significance ($P=.07$); the WMH-L group performed more slowly than the WMH-N group (see Table 3 for complete list of results).

To test for a potential age × WMH interaction, participants were stratified into 2 age groups (<65 years vs ≥65 years); results indicated that the WMH effect was larger among older participants than younger ones only for the visual scanning and motor speed factor ($P=.01$ vs $P=.23$).

We also examined qualitative measures of new learning, which included separate analysis of the easy and hard learning conditions in the acquisition stage. There were marginally significant differences, where the WMH-L group did significantly worse for both easy test items ($P=.05$) and hard test items ($P=.09$). Further analyses of the retention condition of paired associates indicated significant forgetting among the WMH-L group compared with the WMH-N group ($P=.04$). These results were largely driven by decreased retention of hard test items by the WMH-L group (easy items, $P=.72$; hard items, $P=.02$).

COMMENT

Our principal finding was that, within a large, relatively young, nondemented community-based population, individuals with large WMH volumes performed significantly worse on measures of visual organization, attention, planning and initiation of complex activity, and new learning, particularly for more difficult verbal material as compared with those with WMH-N volumes. Although we found that the WMH-L group's performance on the Visual Reproductions–immediate recall task only was of borderline significance ($P=.10$), it is one of the components of the visuospatial memory and organization factor and suggests possible deficits in perception, attention, and concentration, executive functions necessary to perform this test. Marginally significant findings for Trails A ($P=.07$) also lend support to the potential deficits in attention. Our pattern of results supports other studies that have indicated that cognitive deficits associated with WMH are suggestive of subcortical frontal system involvement.[15-17,33,34]

Our analyses were limited to global measures of WMH volumes. There is conflicting evidence suggesting regional WMH and specific cognitive domains. Several studies[15,16,18] suggest that increased WMH volume in the frontal region is linked to processing speed and cognitive flexibility, tasks associated with executive functioning. Gunning-Dixon and Raz,[16] however, did not find a similar association between frontal WMH volumes and working memory. In contrast, Tulberg et al[17] reported that all regional measures of WMH were associated with poorer performance on executive function tests. These discrepancies likely reflect methodologic differences, as recent evidence finds that WMH formation is a generalized process and WMH volumes in one brain region are highly correlated with total WMH volume and WMH in other brain regions.[35]

These results support the notion that the cognitive deficits of WMH are likely the manifestation of asymptomatic cerebrovascular vascular disease. Jeerakathil et al[28] reported that the Framingham Stroke Risk Profile and the individual measure of systolic blood pressure were significant predictors of WMH-L for participants drawn from this same Framingham Offspring Cohort. Similarly, DeCarli et al[26] found larger WMH volume in participants who also had an infarction on MR imaging than in participants without such infarctions. In another study, similar patterns of cognitive impairments were linked to brain atrophy significantly associated with increased Framingham Stroke Risk Profile scores.[36]

Although the availability of cognitive performance measures taken at the time of MR imaging in this relatively younger cohort is a key strength of this study, several limitations restrict the generalizability of these data. The Framingham Offspring Cohort lacks ethnic diversity because their parents, the original cohort, were predominantly Anglo-American, which was representative of the population of Framingham, Mass, at the inception of the study. The exclusion of participants who refused MR imaging or were claustrophobic also decreases the representativeness of this cohort. In addition, the bias introduced by the inability to include participants with pacemakers may serve to underestimate the cases of WMH-L if the relationship between cardiovascular risk factors and WMH is true, as we contend.

Our findings, however, support the growing literature focused on the clinical consequences of age cohort differences in brain morphologic characteristics. We argued that risk factors for vascular disease are tied to the presence of WMH, and that these same risk factors are associated with subtle 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.[37-39] 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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