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White Matter Hyperintensity and Cognitive Functioning in the Racial and Ethnic Minority Cohort of the Framingham Heart Study

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Key Words
White matter hyperintensities · Cognition · Executive function · Framingham Heart Study · Magnetic resonance imaging · Cultural/ethnic diversity

Abstract
Background: Previous studies have demonstrated an association between white matter hyperintensities (WMH) and cognitive performance primarily in Caucasian samples, limiting generalizability to other ethnic and racial groups. This study investigated the association of WMH and cognition in an ethnic and racial minority cohort (Omni) of the Framingham Heart Study and compared these results to the Caucasian (Offspring) cohort. ***Methods:*** Quantitative brain MRI and neuropsychological evaluations were performed on stroke- and dementia-free participants. Cognitive assessment included verbal memory, visuospatial memory and organization, language, and executive functioning. Linear regression models were conducted to assess the association between WMH and cognitive function. ***Results:*** The Omni group presented with demographic factors that significantly differed from those of the Offspring group: they were younger, but had more stroke risk factors such as hypertension. In the Offspring group, WMH volume was significantly associated with poorer performance on tests of executive function and visual organization. No significant associations between WMH and cognitive measures were found in the Omni group, but no differences (significant interaction terms) were seen between the regression coefficients. ***Conclusions:*** The Omni cohort had greater variability in factors that may mediate the association of WMH and cognition. More research is needed to investigate how stroke risk factors impact on the occurrence of WMH and its association with cognition in more diverse cohorts.

Introduction

Vascular factors resulting in cerebrovascular disease are related to cognitive decline in individuals without neurodegenerative disease. In particular, multiple studies have found associations between stroke risk factors and impairments in memory [1, 2] and executive functions [1–5]. Some studies have additionally demonstrated that stroke risk factors such as high blood pressure and diabetes can lead to general cognitive impairment [2, 6] and dementia [7, 8]. The specific causes of cognitive impairment resulting from cerebrovascular disease are un-

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known, but one potential marker of the resulting neuropsychological impairment is damage to subcortical white matter tracks seen on MRI in clinically asymptomatic individuals as white matter hyperintensities (WMH).

WMH are associated with decrements in cognitive functions associated with the frontal lobes including psychomotor speed, attention, and organization as well as with memory functions [9–16]. One study that examined regional white matter and cognitive performance over the adult lifespan demonstrated that frontal white matter was associated with tasks of memory and executive functioning, and that the relation between age and neuropsychological performance may be mediated by frontal lobe white matter [17].

Few studies, however, have examined the association of white matter changes and cognitive impairment in ethnic minority cohorts, despite evidence that some groups may present with greater vascular risk factors implicating the possibility of more severe vascular pathology and resulting cognitive impairment in those groups [18]. One recent study based on an ethnic minority cohort did examine WMH and cognition and found that WMH volume significantly predicted performance on tasks of psychomotor functioning and cognitive flexibility [19]. This study included individuals from Caucasian, Hispanic and African American ethnicities. However, the study only examined the association of WMH to executive functioning and not to other neuropsychological domains such as memory and visuospatial functioning. In addition, the ethnic minority groups were combined in all analyses despite the differential stroke risk factors that have been found in African American, Hispanic, and Caucasian individuals [20]. Another study that examined WMH in African-Caribbean individuals in comparison to Caucasians found that the African-Caribbean participants exhibited greater parieto-occipital white matter lesion volumes and also displayed poorer performance on tests of executive function [21]. This study was also limited by using a single ethnic minority cohort and only examining performance on a task of executive function despite evidence of a more widespread influence of WMH on cognition.

The current study examines an extension of the original Framingham Heart Study Offspring cohort, which was predominantly Caucasian and reflected the population of Framingham, Mass., USA, at the time of the enrollment of the original Framingham study cohort. In the last decade, there has been an effort to recruit ethnically diverse participants in order to examine the generalizability of the reports that were based on the predominantly Caucasian cohort. Therefore, the aim of this study is to determine whether previously reported associations between brain volume, WMH, and neuropsychological test performance apply to the ethnic minority cohort of the Framingham Heart Study.

Participants and Methods

Study Participants

The Framingham Study Offspring cohort was enrolled in 1971 and has had 7 follow-up evaluations over a 30-year period. The current study encompasses neuropsychological testing and brain MRI which took place from 1999 to 2004 on a subset of the surviving members of the Offspring cohort. Of the 2,187 Offspring participants who agreed to partake in the neuropsychological testing and brain imaging, 2,161 were included in the current analyses. The remaining 26 participants were excluded based on consensus review process which determined the presence of clinical stroke [22], probable dementia [23], or other neurologic conditions [20]. The Offspring group was significantly younger than the Omni group, so for the current study, we only include subjects who are $\geq$55 years old, bringing the sample size to 1,582 Offspring participants.

Since the inception of the Framingham Heart Study, the racial and ethnic composition of Framingham and the surrounding towns has changed. For example, by 1990, 10% of the Framingham population was Hispanic and the numbers of non-Hispanic African Americans and Asians was also increasing. Hence, the Heart Study undertook recruitment of minority residents of the Metro west area to reflect the diversity of the Framingham community and to help identify whether findings from one population subgroup generalize to other subgroups. In 1994, the Framingham Heart Study began recruitment of men and women between the ages of 40 and 74, consisting of Hispanic, non-Hispanic black, Asian, and Native-American residents of Framingham and 24 surrounding towns.

For as many as 24% of adult Hispanic residents of Framingham, English was not the primary language, therefore, recruitment, clinical evaluation and neuropsychological testing of these subjects was facilitated by bilingual/bicultural examiners. The current study did not include participants for whom the neuropsychological testing was not done in English, as the aim of this study is to relate the previously reported findings of the Offspring cohort to those of the Omni cohort and validity testing has yet to be done on this subset data. Since the current study involved cohort comparison analysis of factors that are closely related to age, only participants of age 55 and older were included in the study in order to minimize age differences between the groups. 113 ethnic minority participants had MRI data and met the inclusion criteria for this study, of which 48.7% were African American, 21.2% were Hispanic, 28.3% were Asian/Pacific Islander and 1.8% were others. The exclusion criteria applied were the same as those for the Offspring cohort, excluding 7 participants for stroke, dementia, and other neurological conditions. The institutional review board at Boston University School of Medicine, Boston, Mass., USA, approved the study protocol and all participants provided informed consent.

MRI Measures

The methods for MRI acquisition, brain volume assessment [24] and WMH volume quantification [25] have been previously described. The same MRI methods were used for the Offspring and Omni participants. WMH volume was divided by the total cranial volume (TCV) (and multiplied by 100) and log-transformed. The log-transformed WMH volume (LWMHIV) was considered as a continuous variable in the current analysis.

Neuropsychological Test Battery

The neuropsychological assessment was a comprehensive battery including tests of verbal learning and memory (Wechsler Memory Scale-III Logical Memory and Paired Associates), visual memory (Wechsler Memory Scale-III Visual Reproduction), abstract reasoning (Wechsler Adult Intelligence Scale-III Similarities), visuospatial organization (Hooper VOT), language (Boston Naming Test) and executive functioning (Trails A and B).

Statistical Analysis

χ^2 tests for categorical variables and t tests for continuous variables were used to compare the demographic and clinical characteristics between Offspring and Omni, and to compare the three racial subgroups within the Omni population. Natural log transformations were used to normalize the skewed distributions of Trails A and B, Trail B minus Trail A, Boston Naming, and Hooper VOT. The neuropsychological scores used in the analyses are standardized residuals from sex-specific regression analyses adjusting for age and education. To assess the relationship between individual cognitive measures and WMH, linear regression analyses were performed separately for the Offspring and Omni groups. Regression coefficients were reported for each individual cognitive measure score, representing the change in the score for one unit of change of LWMHIV. To examine whether the regression coefficients of WMH between the Omni and Offspring groups are significantly different, we used an omnibus model where cognitive performance served as the outcome, with WMH volume as the predictor variable, a group indicator variable (Omni is the reference group), and an interaction term (group × WMH volume).

Results

The demographic and clinical variables for this subset of participants can be found in table 1. The Omni participants were significantly younger, had larger total cerebral brain volume (TCBV), had smaller WMH/TCV ratio, had significantly less WMH, and were more likely to have hypertension but less likely to be smokers than the Offspring participants. Table 2 shows the demographic and clinical characteristics for African American, Hispanic and Asian/Pacific Islander participants within the Omni cohort. The three groups were significantly different in age, with the African American and Pacific Islander/Asian groups being older than the Hispanic group. In addition, the Hispanic group had the largest TCBV, followed by the African American and then the Pacific Islander/Asian group.

Table 1. Characteristics comparison between Offspring and Omni ≥55 years of age

	Offspring (n = 1,582)	Omni (n = 113)	p value
Age at NP[1]	65.86 ± 7.06	63.82 ± 6.40	0.0028
TCBV[1]	77.27 ± 7.02	78.17 ± 3.34	0.004
SBP, mm Hg[1]	127.44 ± 18.21	128.45 ± 17.30	0.5689
Male	753 (47.60%)	48 (42.48%)	0.2922
SCI	191 (12.11%)	9 (7.96%)	0.1874
Hypertension	284 (16.12%)	39 (34.51%)	<0.0001
Diabetes	95 (6.32%)	11 (9.73%)	0.1568
Smoking	227 (15.11%)	14 (12.39%)	0.04332
LWMHIV[1]	−7.473 ± 1.037	−7.76 ± 1.112	0.005

NP = Neuropsychological testing; SBP = systolic blood pressure; SCI = silent cerebral infarct. [1] Mean ± SD.

As expected, in the Offspring group, WMH was significantly associated with a test of executive functioning (Trail B – Trail A; $\beta = 0.07$, $p < 0.01$), indicating that higher WMH volume is associated with longer time to complete the task. WMH was also associated with a test of visual organization (Hooper VOT; $\beta = -0.06$, $p < 0.01$), indicating that greater WMH is related to poorer performance on this measure (table 3). In the Omni group, no significant associations between WMH and cognitive testing were found. There were no significant interactions between the Omni and Offspring groups in regard to the relation between WMH and cognition, indicating similar effects for both groups, although this may be due to low power in our sample.

Given the significant group differences in some stroke risk factors including smoking and hypertension, the analyses were repeated controlling for stroke risk factors. When controlling for smoking, diabetes and hypertension, there were no changes to the above findings. Although the regression coefficients and p values did change slightly, the conclusions of the regression analyses remain the same. Significant associations between WMH and Trail A–B and Hooper VOT remained in the Offspring group while no significant associations between WMH and cognition were found in the Omni participants. Finally, no significant interaction terms were found, again demonstrating that the effects in the two groups are similar.

Table 2. Characteristics of study sample in the first Omni examination

	Omni (n = 113)			
	African American (n = 55)	Hispanic (n = 24)	Asian and Pacific Islander (n = 32)	p value
Age at NP[1]	64.69 (6.60)	60.20 (5.00)	64.65 (6.03)	0.0082
TCBV[1]	77.87 (3.39)	80.73 (2.70)	76.84 (2.79)	<0.0001
SBP, mm Hg[1]	128.45 (16.90)	125 (20.64)	124.51 (13.66)	0.6013
Male	20 (36.36%)	10 (41.67%)	18 (56.25%)	0.1930
SCI	5 (9.09%)	2 (8.33%)	1 (3.13%)	0.6272
Hypertension	20 (36.36%)	8 (33.33%)	10 (31.25%)	0.8843
Diabetes	6 (10.91%)	3 (12.50%)	2 (6.25%)	0.7694
Smoking	10 (18.18%)	1 (4.17%)	3 (9.38%)	0.2293
LWMHIV[1]	–7.631 (1.209)	–7.924 (1.080)	–7.896 (–0.947)	0.4241

NP = Neuropsychological testing; SBP = systolic blood pressure; SCI = silent cerebral infarct. [1] Mean values with SD in parentheses.

Table 3. Associations between neuropsychological variables and LWMHIV in Offspring and Omni participants separately

Neuropsychological measure	Stratified analysis				Omnibus model
	Offspring (n = 1,582)		Omni (n = 113)		Offspring and Omni combined (n = 1,695)
	β-coefficient	p value	β-coefficient	p value	interaction p value
LM immediate recall	0.002	0.941	0.025	0.779	0.793
LM delayed recall	0.0003	0.991	0.052	0.564	0.566
Visual Reproduction immediate	–0.042	0.090	–0.080	0.356	0.680
Visual Reproduction delayed	–0.038	0.125	–0.013	0.873	0.786
Paired associated learning immediate	–0.014	0.572	0.025	0.772	0.658
Paired associated learning delayed	–0.016	0.516	0.050	0.582	0.472
Trail making A[1]	–0.010	0.681	–0.075	0.394	0.484
Trail making B[1]	–0.029	0.260	–0.091	0.318	0.498
Trail B – Trail A[1]	0.068	0.012	0.011	0.916	0.566
Similarity	0.024	0.340	–0.012	0.880	0.691
Boston Naming Test[1]	0.005	0.847	0.066	0.442	0.497
Hooper VOT[1]	–0.061	0.012	0.046	0.595	0.227

Regression coefficients (β) and p values are reported. Interaction p value for differences between Offspring and Omni are also reported. LM = Logical Memory. [1] Based on log-transformed data.

Discussion

The findings from the present study are among the few contributions to the literature on the relation between WMH and cognitive functioning in ethnically and racially diverse populations. These findings extend previous reports, which primarily used Caucasian samples, to a diverse group of individuals living within the United States. Following up on Au et al. [9], we found that in an age-comparable (55 years and older) subset of the Offspring cohort, higher WMH is a predictor of performance on tests of executive function and visuospatial organization; no such associations were seen in the ethnically diverse cohort. The majority of the effect sizes for each of the cognitive measures were similar in the Offspring and Omni groups, indicating that no differ-

ences were found in the impact of WMH on cognitive performance. Only a test of visuospatial organization showed some indication of WMH having a different or opposite effect on the Omni in comparison to the Offspring cohort, where greater WMH predicted lower performance on the task in the Offspring but not the Omni group.

In this sample of racially and ethnically diverse individuals, the cumulative effect of various stroke risk factors may impact the association of WMH and cognition in a way that is different than is seen in a Caucasian sample. Most research in Caucasians has shown that the combination of factors of older age, hypertension, and smoking can lead to greater risk of stroke, WMH, and cognitive impairment [26]. In the current study, the Omni cohort was significantly younger, had lower occurrence of large WMH, and had a greater proportion of individuals with hypertension but fewer smokers compared to the Offspring cohort. While their younger age is typically associated with less WMH and better cognitive performance, the Omni cohort had higher rates of hypertension, which has been associated with decrements in cognitive performance in other studies. Having a greater proportion of individuals with hypertension may put the Omni group at greater risk for both WMH and subsequent cognitive decrements at a later age, which longitudinal follow-up will determine. Alternatively, a higher rate of smoking in the Offspring cohort, though not associated with lower cognitive performance per se, is a significant stroke risk factor and may impact cognitive performance and WMH by its effects on the cardiovascular system. Although our follow-up covariate analysis examining the impact of these stroke risk factors did not change the results significantly, with the small sample size of our Omni group, significant impact of the stroke risk factors on our findings may have been obscured. Thus the differential impact of these risk factors on the associations between WMH and cognition in Caucasian and ethnic minorities should be explored further in future studies.

There are limitations to this study that may account for why we did not see an association between WMH and neuropsychological variables such as executive functioning and memory consistent with previous reports. The Omni group in the current study had a smaller sample size than the Offspring group, resulting in a decrease of power to detect potentially significant associations. In addition, the power in our analyses was reduced by using WMH as a continuous variable, not as a binary variable as was done in our previous report [9]. This may account for differences seen between the outcomes in the current Offspring sample in comparison to those reported by Au et al. [9]. Limited sample size also prevented us from examining the impact of WMH on cognition in each of the ethnic groups individually.

The Omni cohort is not only ethnically diverse, but also contains variability in the different factors that may mediate the association of WMH and cognition. In this regard, more research is needed to investigate how hypertension and other stroke risk factors impact on both the occurrence of WMH and its association with cognition in more ethnically diverse cohorts. These findings will be important in order to further elucidate whether there are differences in these associations between Caucasians and other cohorts.

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