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A bivariate genetic analysis of cerebral white matter hyperintensities and cognitive performance in elderly male twins

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Abstract

White matter hyperintensities (WMHs) are frequently observed on MRI scans of elderly nondemented people and have been associated in the past with cognitive impairment and physical dysfunction. Individual differences in the prevalence and severity of WMHs have been documented and more recently we reported on the significant contribution of genetic influences to this variability. The objective of the present study was to further investigate, in the context of a behavioral genetic paradigm, the nature of the association between WMHs and cognitive and physical function. MRI brain scans and a battery of neuropsychological and physical function tests were given to 142 male-male twin pairs [72 monozygotic (MZ) and 70 dizygotic (DZ)] participants in the 4th exam of the NHLBI Twin Study. Biometric genetic modeling was used to estimate the genetic and/or environmental covariation between WMHs and cognitive and physical summary scores. The phenotypic association between WMHs and cognitive function in this sample of twins was modest but statistically significant. Genetic analyses of cognitive and physical function summary scores found that 55% to 70% of the observed variability was due to genetic influences. A further decomposition of the phenotypic association between WMHs and cognitive function found that 70% to 100% of the phenotypic covariation was due to common genetic effects. Similar results explained the association between WMHs and performance on two physical function tests. We conclude from these analyses that common genetic influences explain to a large extent previously observed phenotypic associations between large amounts of WMHs and poor cognitive and physical function in the elderly.

Keywords: White matter hyperintensities; Cognition; Genetics; Twins; Elderly

1. Introduction

White matter hyperintensities (WMHs) are frequently seen on MRI scans of nondemented elderly and are thought to precede cortical atrophy observed in Alzheimer's disease and vascular dementias [1]. When located in the deep subcortical areas, WMHs are thought to reflect ischemic damage resulting in focal rarefaction of myelin, loss of fibers, and in some cases, lacunar infarctions [2–4]. Among the most robust correlates of WMHs is old age [1,5], although individual differences in prevalence and severity of WMHs have been documented in a number of large population studies of older people [6,7]. The sources of this variability in WMHs are not sufficiently understood and recently we were the first to report on the significant contribution of genetic influences to the variability in WMHs in a large sample of older male twins [8–10]. We also observed for this group significant associations between WMHs and poor executive and physical function and documented the presence of synergistic effects between the ApoE $\epsilon 4$ allele and extensive amounts of WMHs on subjects' risk for 10-year decline in cognitive performance [9].

The contribution of genetic influences to cognitive function in the elderly has been previously documented in other large samples of elderly twins [11–13] and was confirmed in our own studies for an extensive battery of cognitive and physical function tests [14,15]. No study, however, to date has attempted to quantify the genetic overlap between struc-

Abbreviations: AIC = Akaike information criterion; CSF = cerebrospinal fluid; MRI = magnetic resonance imaging; MZ = monozygotic; DZ = dizygotic; NHLBI = National Heart, Lung, and Blood Institute; WMHs = white matter hyperintensities.

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tural brain changes such as WMHs and cognitive or physical performance in the elderly.

The objective of this study was to use the behavioral-genetic paradigm to explore the nature of association between WMHs and cognitive and physical performance. In addition, we were specifically interested in estimating the relative contribution of genes associated with WMHs to the genetic variance in cognitive and physical function.

2. Methods

2.1. Study population

Data for this study were collected in an ongoing investigation of the genetic and environmental influences on brain structure and function in the NHLBI Twin Study [14,16,17]. Originally, the NHLBI Twin Study was designed as a longitudinal study of cardiovascular disease (CVD) and associated CVD risk factors in 514 pairs of male twins, 254 monozygotic (MZ) and 260 dizygotic (DZ). Twins in this study are World War II veterans, born during 1917–1927 and 42 to 56 years old when first examined in 1969–1972 [18]. Three follow-up examinations, after 10, 16, and 25 years, assessed CVD status and collected repeat measurements of physiological, biochemical, and psychosocial risk factors. In the most recent follow-up (1995–1997) of the NHLBI Twin Study, brain MR imaging and a comprehensive battery of cognitive function tests were given to these subjects. Analyses in the present study are limited to intact twin pairs who participated in the fourth examination cycle of the NHLBI Twin Study and for whom MRI and cognitive and physical function data were available. The final sample for analysis consisted of 142 intact pairs [72 MZ pairs and 70 DZ pairs], mean age 73 $\pm$ 3 years (range 69 to 80) when MRI brain scanned.

2.2. Cerebral MRI scans and image analysis

MRI (1.5 T) scanning on GE scanners was performed at four study sites using a conventional spin-echo, double-echo sequence in the axial orientation with TR = 2000, TE = 20/100, 24 cm field of view, and 5 mm contiguous slices from the vertex to the foramen magnum imaged in a 256 $\times$ 192 matrix and interpolated to 256 $\times$ 256 with one excitation. Axial images were angled to be parallel to the anterior commissure-posterior commissure line. After acquisition of the MRI scans, the digital information was transferred to a central location for processing and analysis. Volumetric analysis of the MRI scans was performed with a custom-written program operating on a Sun Microsystems Ultra 1 workstation. Image evaluation was based on a semi-automated segmentation analysis that involves operator-guided removal of nonbrain elements, as previously described [19]. For segmentation of brain parenchyma from cerebrospinal fluid (CSF), a difference image was created by the subtraction of the second-echo image from the first-echo image. Image intensity nonuniformities were then removed from the difference image, and the resulting corrected image was modeled as a mixture of two Gaussian probability functions [19,20]. The segmentation threshold was determined at the minimum probability between the modeled CSF and brain matter intensity distribution [21]. For segmentation of WMH from brain matter, the first- and second-echo images were summed, and, after removal of CSF and correction of image intensity nonuniformities, a lognormal distribution was fitted to the summed image data. A segmentation threshold for WMH was determined a priori as 3.5 standard deviations in pixel intensity above the mean of the fitted distribution of brain parenchyma. Intra- and interrater reliabilities of this method have been published [19].

Of the total number of 498 individual twin participants in the 4th exam cycle, 81 (16%) did not have the MRI exam. Of these 81 subjects, 37 did not meet inclusion criteria, 17 attempted MRI but had a claustrophobic reaction in the scanner, 25 were home visits, and only two subjects refused the MRI exam. Compared to individuals with MRI those without MRI did not differ significantly on age, years of education, and MMSE score. Mean age of twins in the present analysis was 72.5 $\pm$ 2.9 years and on average they had 1 year of post-high school education, or 13.5 $\pm$ 3.2 years. Average systolic blood pressure was 138.0 $\pm$ 18.0 mm Hg and average diastolic blood pressure was 75.7 $\pm$ 9.5 mm Hg, and 32% of the twins were on antihypertension medications when MR scanned. Many, 64%, ever smoked (mean number of years smoked, 19.5 $\pm$ 19.8 years) and many subjects consumed alcohol regularly (mean number of alcoholic drinks per week, 6.5 $\pm$ 2.9).

2.3. Performance measures

Cognitive function tests given at the time of MRI testing and included in the present analysis were: (1) Color-Word Interference (number of correct colors identified in 45 s during the interference trial; participants reporting difficulty with color perception were not given the test) [22]; (2) Verbal Fluency (total number of correct words generated in three one-minute trials) [23]; (3) Digit Symbol Substitution (number of correct digit-symbol pairings in 90 s) [24]; and (4) Trail Making A and B (seconds to completion) [25]. Each of these four neuropsychological tests is considered an index of executive control requiring several cognitive and perceptual-motor functions, including sustained attention, visual perception, and short-term memory [26–28].

Previous studies in aging twins and our own studies of the NHLBI twins provide evidence for the presence of significant genetic variance for at least one index of executive control, the Digit Symbol Substitution task [11–13]. More recently, we used the methods of multivariate genetic analysis to determine the contribution of genetic and environmental influences on four different tasks of executive

control in the NHLBI Twin Study [29]. Our results revealed that a reduced common pathway model with a latent "executive control" factor fits the observed data adequately. This common "executive control" latent factor had a heritability (i.e. percent of genetic variance) of 79% and contributed substantially to the genetic variance in performance on each individual test separately. In addition, of the four tests examined, Digit Symbol Substitution appeared to be the strongest marker of executive control while Verbal Fluency stood out as displaying a pattern of both genetic and shared environmental influences distinct from the other three measures of executive control [29]. Apart from the "executive control" latent factor we used the Mini-Mental State Exam (MMSE) as a measure of global mental functioning.

Physical function was assessed with three independent measures of lower extremity function, including a timed repetitive chair stand, a timed 8-foot walk, and a standing balance task [15]. Categories of performance were created for each set of performance measures. For the 8-foot walk and repeated chair stands, those who could not complete the task were assigned a score of 0. Those completing the task were assigned scores of 1 to 4, corresponding to the quartiles of time needed to complete the task in a large representative sample of older adults, and with the fastest times scored being 4. Similarly, the three tests of standing balance were considered as hierarchical in difficulty and were assigned a single score of 0 to 4. Summing the single-category scores for the 8-foot walk, chair stand, and standing balance tasks we created a lower-extremity summary score [15].

We assessed neuromuscular performance by measuring grip strength with an adjustable mechanical hand dynamometer (Lafayette Instrument Company, Lafayette, Indiana). Three trials, with brief pauses, were allowed for each hand alternately and the best result of the three trials was chosen for analysis.

2.4. Genetic analyses

The general twin model assumes three sources of phenotypic variance: additive genetic effects (abbreviated A), shared or common environmental effects (C), and nonshared environment effects (E). Common environment refers to nongenetic factors that make co-twins similar to one another. These will include the uterine environment, the rearing environment, the frequency of contact between twins, and their joint exposure to the same social and cultural environment. Nonshared environmental influences are all the factors (e.g. accidents, illnesses, individual behaviors) that make members of a twin pair different from one another.

The relative contributions of genetic and environmental influences are estimated by maximum likelihood methods that calculate the negative log-likelihoods (-LL) of different models using the software Mx [29]. The goodness of fit of a model is tested using chi-square (χ^2) tests. Hierarchic tests are used to compare the goodness of fit of nested models (e.g. the AE model and CE model to that of a full ACE model). Twice the difference in log-likelihoods (-2LL) between the AE and the ACE model is distributed as χ^2 with 1 degree of freedom (df) so if χ^2 (df = 1) was smaller than 3.84 (not significant; $P > 0.05$), then omitting common environmental influences (in the AE model) was assumed to lead to no deterioration in fit. Utilizing this principle of parsimony the most restrictive model was accepted as the best-fitting one.

In the results section of this paper we present parameter estimates for the best-fitting model, together with 95% confidence intervals for the estimated heritability (i.e. percent genetic variance of total variance). We used the notations h^2 to symbolize the proportion of variance due to additive genetic effects and c^2 and e^2 to symbolize shared and nonshared environmental effects, respectively [30].

Following the univariate genetic analyses, we used bivariate genetic analysis to estimate the genetic and environmental overlap between WMHs and cognitive and physical performance scores. Because the AE model shows the best fit in the univariate genetic analyses, we used this model as the full model in all the bivariate analyses. Fig. 1 shows a bivariate AE model for one member of a twin pair, where A_c and E_c are the genetic and environmental influences common to WMHs and function, and A_s and E_s are the genetic and environmental influences specific to cognitive or physical function. The effects of A_c and E_c on WMHs are represented by parameters h_c and e_c, and the effects of A_c and E_c on function are represented by parameters h_c' and e_c'. To test the significance of overlapping genetic and/or environmental factors, parameters h_c and h_c' and e_c and e_c', respectively, were constrained to zero. To test the significance of genetic and environmental factors specific to cognitive or physical function, parameters h_s and e_s were constrained to zero. Submodels that were nested in each other were compared by hierarchical χ^2 tests. The genetic correlation r_g was calculated from the path coefficients shown in Fig. 1 using the formula $r_g = h_c h_c'/h_c\sqrt{h_c'^2 + h_s^2}$. All the bivariate genetic analyses were conducted within a structural equation framework and should be viewed as exploratory in nature.

3. Results

Before performing the genetic analyses, we screened all variables for outliers and tested each distribution for deviation from normality. There was no deviation from normality in the distribution of cognitive and physical function scores, so the data were left untransformed. The distribution of WMHs, however, was positively skewed, so that log transformed values were used in all subsequent biometric analyses. Table 1 lists twin-pair correlations by zygosity and presents maximum-likelihood estimates of the genetic (h^2)

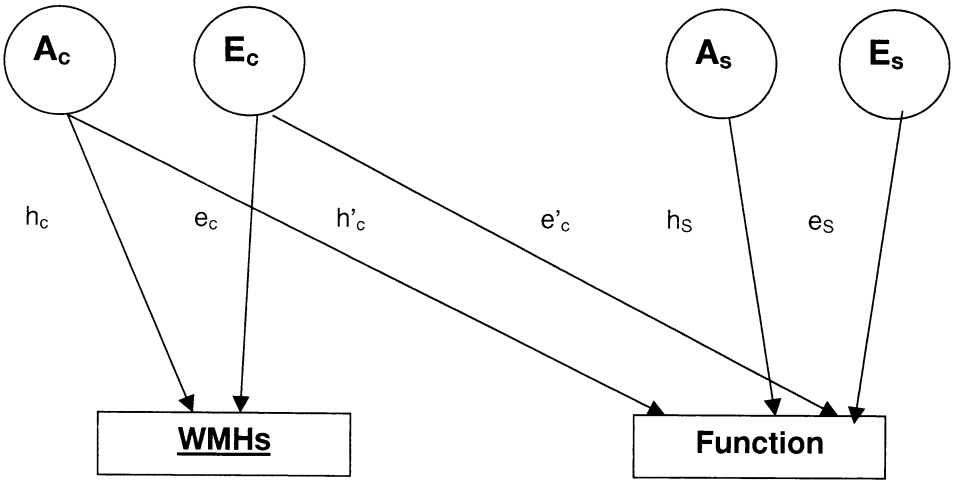

Fig. 1. Bivariate genetic model. A_c and E_c are genetic and nonshared environmental influences common to WMHs and cognitive performance; A_s and E_s are genetic and nonshared environmental influences specific to cognitive performance. The effects of A_c and E_c are represented by parameters h_c, e_c and h'_c, e'_c, respectively; specific A_s and E_s effects are represented by parameters h_s and e_s.

and the environmental (e^2) components of variance for each cognitive and physical functioning test score.

The best-fitting univariate model for each of the cognitive and physical function summary scores was a model consisting of two latent factors: genetic (A) and nonshared environmental (E) factors. When tested against a full univariate ACE model, the common environmental parameter (c^2) could be dropped from the model without reduction of model fit. We concluded that the AE model fits the data best, and heritability estimates with corresponding 95% confidence intervals were calculated as represented in Table 1.

In the bivariate genetic analyses, we used the model depicted in Fig. 1, where the association between WMHs and function is assumed to be due to overlapping genes and/or overlapping environmental influences. In addition, independent genetic and environmental effects not shared with WMHs are assumed to contribute to the variability in function scores. First, the full AE model of Fig. 1 was fitted to the observed WMHs-function variance-covariance matrices. Then, estimated parameters that were close to zero were dropped to arrive at the most parsimonious model fitting the data. The best-fitting model was selected by change in chi-square from the full model to the submodel tested with the degrees of freedom equal to the difference between the two models. A significantly worse fit would be indicated by a change in chi-square that was positive and significant greater than 3.84.

Fig. 2A portrays the best bivariate genetic model fitting the covariation between WMHs and "executive function" factor scores. We found reduction in fit when either the genetic (h_c and h'_c) or environmental (e_c and e'_c) parameters were set to zero. The corresponding log-likelihood statistics were $\Delta\chi^2$ (1) = 3.90 and $\Delta\chi^2$ (1) = 3.86, respectively. We concluded that the full AE model is the best model fitting these data [χ^2 (14) = 9.07, p = 0.83]. Using the full AE model, we estimated that 70% and 30%, respectively, of the phenotypic association between WMHs and executive func-

Table 1
Genetic and environmental influences from univariate analyses of performance measures associated with WMHs. Subjects are 72 MZ pairs and 70 DZ pairs from the fourth exam of the NHLBI Twin Study

	Twin-pair correlations		Parameter estimates[b]		Model fit			Confidence interval 95% CI[c]
	R_{MZ}	R_{DZ}	h^2	e^2	χ^2	df	*p*-value	
Cognition								
Executive function	0.71	0.40	0.70	0.30	5.13	4	0.27	[0.52, 0.91]
Mini-Mental State Exam	0.46	0.15	0.40	0.60	5.75	4	0.22	[0.27, 0.65]
Physical function	0.57	0.20	0.55	0.45	1.91	4	0.75	[0.36, 0.78]
Hand-grip strength	0.69	0.45	0.71	0.29	2.87	4	0.58	[0.52, 0.91]
WMHs[a]	0.74	0.30	0.74	0.26	1.21	4	0.88	[0.55, 0.96]

[a] Log transformed.
[b] Standardized estimates expressed as percentage of total variance.
[c] CI = confidence interval for the heritability estimate h^2.
Note: Parameter estimates and model fit statistics (chi-square and *p*-value) are shown for the univariate genetic model best fitting the observed data.

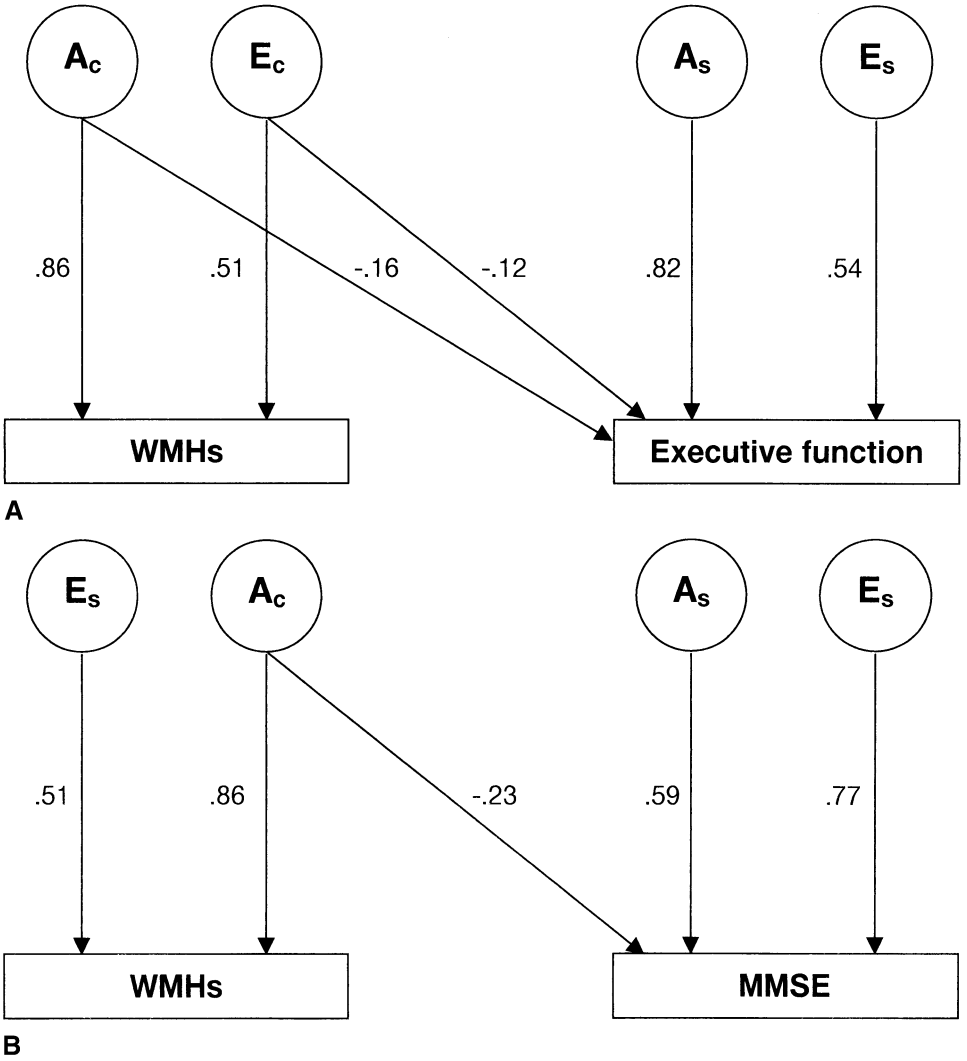

Fig. 2. Path diagram representing the bivariate fitting results for a) WMHs and executive function scores and b) WMHs and MMSE scores. Latent variables are represented by circles and phenotypes are represented by boxes. A_c and E_c are genetic and nonshared environmental influences common to WMHs and cognitive performance; A_s and E_s are genetic and nonshared environmental influences specific to cognitive performance.

tion scores is due to overlapping genetic and environmental influences.

Fig. 2B depicts the best bivariate genetic model fitting the covariation between WMHs and MMSE scores. The χ^2 statistic for the full model was χ^2 (14) = 15.48, p = 0.35 and that of a reduced model with common environment set to zero was χ^2 (15) = 15.71, p = 0.40. Because the log-likelihood difference between these two models is $\Delta\chi^2$ (1) = 0.23 is not significant, the common environmental parameter can be dropped from the model without loss of fit. As a result, 100% of the covariation between WMHs and MMSE is due to overlapping genetic effects. Similarly, we found that the best-fitting bivariate models depicting the relationship of WMHs to lower physical functioning and hand-grip strength was a bivariate genetic model, with 100% of the covariance accounted for by overlapping genetic and not overlapping environmental effects. Goodness-of-fit statistics for the best-fitting models were χ^2 (15) = 8.95, p = 0.88 for the covariation between WMHs with lower physical functioning and χ^2 (15) = 9.60, p = 0.72 for the covariation with hand-grip strength.

In Table 2, we list the maximum-likelihood estimates of: (1) the phenotypic correlation $r_{phenotypic}$, (2) the proportions of the phenotypic correlation due to genetic and environmental influences (h*r*h, e*r*e), (3) the genetic and environmental correlations (r_g, r_e), and (4) the proportions of common and specific genetic variance shared and not shared with WMHs.

Although overlapping genes accounted primarily for the phenotypic association between WMHs and function scores, we notice from Table 2 (last two columns) that the contribution of overlapping genes to the genetic variance in cognitive or physical function scores is relatively small. For instance, overlapping genes contribute 8% to the genetic variance in "executive function" and 12% to the genetic variance in MMSE, the remainder of the genetic variance

Table 2
Bivariate analysis of the contributions of genetic and environmental influences to associations of WMHs with cognitive and physical function scores

Cognitive and physical tests[a]	$r_{phenotypic}$[b]	Genetic and environmental correlation				Genetic variance[g]	
		hrh[c]	ere[d]	r_g[e]	r_e[f]	Shared with WMHs	Specific to function
Cognitive function							
Executive function	−0.20*	70%	30%	−0.24*	−0.22*	8%	92%
Mini-Mental State Exam	−0.20*	100%	0%	−0.36**	0.0	12%	88%
Lower physical function	−0.18*	100%	0%	−0.29*	0.0	12%	88%
Hand-grip strength	−0.25*	100%	0%	−0.43**	0.0	22%	78%

* $p < 0.05$; ** $p < 0.01$.

[a] The baseline bivariate model AE comprised common genetic and environmental effects influencing WMHs and performance scores and specific effects influencing only performance test scores.

[b] Maximum-likelihood estimates of the phenotypic correlation between WMHs and performance test scores.

[c] hrh is the percentage of phenotypic correlation due to overlapping genes.

[d] ere is the percentage of phenotypic correlation due to overlapping environmental influences.

[e] Genetic correlation. Significance denotes a significant log-likelihood ratio test when the χ^2 statistic for the model with the common genetic pathway h_c and h_c' fixed to zero is compared with the full model.

[f] Environmental correlation. Significance denotes a significant log-likelihood ratio test when the χ^2 statistic for the model with the common environmental pathway e_c and e_c' fixed to zero is compared with the full model.

[g] Common and specific percentages of genetic variance in performance shared and not shared with WMHs.

being specific to cognitive function. Similarly, 88% and 78%, respectively, of the genetic variance in physical functioning and grip strength is due to genes that are not shared with WMHs.

4. Discussion

Significant associations between large amounts of WMHs and poor cognitive and physical functioning have been previously documented [2,14]. The underlying causes, however, for these associations are unknown. In this study, we used a behavior-genetic approach to investigate the nature of the association between WMHs and cognitive and physical performance in a sample of older male twins. Specifically, we estimated the genetic and environmental correlations between total calculated WMH volume and cognitive and physical function scores and determined the contribution of overlapping genetic influences to the heritability of cognitive and physical performance.

The phenotypic correlation between WMHs and performance scores in this sample of older male twins was modest. Univariate estimates, however, of heritability suggest substantial genetic variance for each of the performance measures in this study. Although a priori there is a stronger motivation to study the genetic covariation between traits that show a high degree of phenotypic covariation, the link between the degree of phenotypic covariation and the degree of genetic covariation is not obvious and in many cases unknown. The pattern of twin correlations reported in Table 2 does not suggest attenuation of the phenotypic covariation between structural brain changes and cognitive and physical function due to ascertainment bias (e.g. selective attrition). Most likely, strong selection for healthier subjects who survived to old age might have attenuated the estimated genetic covariation between WMHs and cognitive and physical function as presented in Table 2.

A compelling finding of the present study is therefore the significant genetic covariation between structural brain changes and cognitive and physical function scores in a healthy cohort of elderly male twins. Given the fact that we currently know very little about the causes of covariation between WMHs and performance, the demonstrable overlapping genetic mechanism between WMHs and poor cognitive functioning provides empiric support that these phenomena may represent a single dimension of the genetics of brain aging.

In the first part of our analyses, we estimated the contributions of genetic and environmental influences to individual differences in cognitive and physical function. Our estimates of heritability in the range of 55% to 70% of the variance are consistent with a growing body of literature suggesting a significant role of genetic influences on cognitive performance in the elderly [17,18,26]. Moreover, 70% to 100% of the phenotypic covariation between WMHs and function scores was due to overlapping genetic influences. Interestingly, we found that overlapping environmental influences contributed significantly to the covariation between WMHs and executive function scores but to none of the other phenotypic relationships between WMHs and cognitive or physical function scores.

Executive functions are controlled primarily by the frontal lobe and subcortical structures that project to the frontal cortex [31]. They include mental flexibility, interference coping and conceptual tracking, which are used to measure attention, speed of processing, and strategy like the verbal fluency test. Significant associations between executive

function tasks and WMHs have been consistently reported in other studies [32–34].

For this cohort, however, overlapping genetic influences between WMHs and executive function scores accounted for only 8% of the estimated heritability in performance. Thus, although genetic influences account for most of the phenotypic association between WMHs and cognitive function, the majority of the genetic variance in cognition appears to be independent from that in WMHs.

The present study was the first to explore the nature of association between WMHs and neuromuscular function. We observed a significant phenotypic association between WMHs and decline in grip strength that was due entirely to overlapping genetic influences and not overlapping environmental influences. Decline in neuromuscular and lower-extremity function is most likely to result from a decline in excitation-contraction coupling, a decline in the activation of high-threshold motor units, or a decrease in the number of fibers [35,36]. In stroke victims, the injury in the central nervous system affects the descending neural pathways and results in poor motor unit activation [37,38]. WMHs and stroke share similar cardiovascular risk factors, and WMHs have been shown to predict future stroke [39,40]. Muscle weakness is one of the manifestations of impaired neurological function after stroke [37]. Therefore, a probable explanation of the significant genetic overlap between WMHs and poor neuromuscular function could be alterations in cerebrovascular autoregulation mechanisms occurring as a result of aging or the presence of undetected silent cerebrovascular disease.

We reported previously for this sample of twins that inheritance of ApoE4 genotype was significantly associated with lower-extremity function without showing an independent association with WMHs [9]. On the basis of these previous and current findings, we suggest that the risk associated with ApoE4 may have occurred through increased neuronal vulnerability determined possibly by genes unrelated to genes that determine subjects' performance on lower-extremity function tests [40].

Finally, results reported in this study need to be interpreted in the context of a number of limitations. First, because of various selection criteria (e.g. World War II veterans; selective participation in the follow-up exams; and attrition of one of the twin subjects in a pair due to death, disease, or nonparticipation), subjects in the present study may represent a somewhat select group that is healthier than the population of U.S. males of this age. If anything, this selectivity may have underestimated the prevalence of WMHs, and could have underestimated the genetic correlation between WMHs and cognitive performance. Second, the fact that the subjects are all men limits the extent to which these results are generalizable to women. Third, we used estimates of total WMH volumes and did not take into account regional (lobar) differences in WMHs. The relationship between WMHs and performance in the elderly may also be nonlinear [10,14,15]. Using total WMH volume instead of threshold values may also have played a role in the estimation of the genetic covariation between WMHs and physical and cognitive functioning. Future work and follow-up MRI brain scans in this sample of twins should clarify the nature of associations observed in the present study.

In conclusion, we found evidence in this study for a genetic overlap between WMHs and performance in normal elderly subjects, suggesting a possible underlying biologic mechanism for previously observed phenotypic associations between MRI findings and performance deficits in the elderly. The present results should also help in refinement of the phenotype, ultimately leading to the identification of specific genes involved in physical and cognitive decline in the elderly.

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