The effect of white matter hyperintensity volume on brain structure, cognitive performance, and cerebral metabolism of glucose in 51 healthy adults

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Article abstract—*Objective:* To assess the association of MRI white matter hyperintensities (WMHI) with cognitive performance, cerebral structure, and cerebral metabolism in 51 healthy individuals aged 19 to 91 years without cerebrovascular risk factors. *Background:* Abnormal white matter signals have been associated with brain atrophy, reduced cerebral blood flow, focal neurologic signs, gait disorder, and poorer neuropsychological test performance. Most studies of WMHI, however, include subjects with hypertension or other identifiable causes of cerebrovascular disease that may have an independent effect on brain structure and function. To assess brain changes associated with WMHI independent of cerebrovascular risk factors, we determined WMHI volume, brain volume, cerebral metabolism, and cognitive performance for a group of subjects free of medical illness. Regional cerebral metabolism and cognitive domains were also assessed to evaluate the possible role of frontal lobe dysfunction in subjects with WMHI. *Design:* Cross-sectional study of 51 very healthy subjects aged 19 to 91 years. *Methods:* WMHI, brain, and CSF volumes were determined by MRI segmentation. Neuropsychological tests were employed to assess multiple cognitive domains. Brain metabolism was determined from 18-fluoro-2-deoxy-D-glucose PET. Multivariate relations were tested with stepwise linear regression. Models included the potential confounders of age and education where appropriate. *Results:* The distribution of WMHI volume was bimodal, with five subjects having WMHI volumes beyond three SDs from the normally distributed population. A WMHI volume of greater than 0.5% of intracranial volume was considered abnormal. Within the multivariate models, WMHI volumes were significantly predictive of increased ventricular volume, reduced brain volume, and reduced cognitive scores. Subjects with greater than 0.5% WMHI volume also had significantly lower frontal lobe metabolism, significantly higher systolic blood pressure, significantly larger ventricular volume, and significantly lower scores on frontal lobe-mediated neuropsychological tests than age-matched controls. *Conclusion:* WMHI volume is associated with structural and functional brain changes even within a group of very healthy individuals. WMHI is associated with poorer frontal lobe cognitive function and, when severe, is accompanied by significantly reduced frontal lobe metabolism. Subjects with large WMHI volumes have significantly higher systolic blood pressure, brain atrophy, reduced cerebral metabolism, and lower scores on tests of frontal lobe function than age-matched controls. Large amounts of WMHI are, therefore, pathologic and may be related to elevated systolic blood pressure even when it is within the normal age-related range.

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Cerebral white matter hyperintensities (WMHI) seen with MRI occur with normal aging, and are more frequent in patients with hypertension and cerebrovascular disease.[1,2] While WMHI are commonly observed, our understanding of how they affect cerebral structure and function continues to evolve. In the nondemented elderly, abnormal white matter signals have been associated with brain atrophy,[3-5] reduced cerebral blood flow,[6-8] focal neurologic signs,[9] gait disorder,[10] and in some[9,11,12] but not all[13,14] studies poorer neuropsychological test performance. WMHI may indicate the presence of ischemic vascular disease when seen in individuals with cerebrovascular risk factors or stroke,[15] but the higher frequency of WMHI in healthy individuals over 50 years of age suggests that WMHI may also

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be a normal age-related phenomenon.[1,3]

Lack of definite conclusions regarding the pathophysiology and clinical significance of WMHI may reflect differences in both subject selection and study methods.[3] First, published reports[1,11,13] of WMHI in normal aging often include subjects with hypertension. Cerebrovascular risk factors can affect brain structure and function independent of the presence or extent of WMHI. For example, hypertension is associated with brain atrophy and reduced cerebral metabolism of glucose,[16-20] even in subjects with mild disease and without significantly more WMHI.[19,20] Second, the greater sensitivity of MRI to detect WMHI may lessen the pathophysiologic significance of WMHI when compared with abnormal white matter signals seen with CT. There have been consistent differences in cerebral structure and cognitive performance when subjects with leukoaraiosis on CT brain images are compared with those without leukoaraiosis.[9] Neuropathologic studies of leukoaraiosis on CT find brain abnormalities in approximately two-thirds of patients studied.[21] The clinical and pathologic findings of WMHI on MRI are, however, more variable.[3,22,23] Some authors[6,11] reconcile the differences between WMHI detected by MRI and leukoaraiosis seen on CT by suggesting that a threshold level of WMHI severity on MRI must be present before functional expression. Third, most studies[1-3,5,9] used a qualitative rating of abnormal white matter. Categoric ratings of WMHI may not allow for valid comparison across imaging modalities and may be insensitive to subtle, but continuous, effects revealed by quantitative measures.

Finally, if one agrees that WMHI adversely affect brain structure or function,[3-9,11,12] the pathophysiology of this effect has yet to be determined. Neuropsychological test performance suggests frontal lobe dysfunction,[11,12] but WMHI are diffusely distributed in the periventricular white matter. Boone et al[11] argue that the cognitive impairment induced by WMHI is nonspecific, and that poorer performance on tests of frontal function results from a multifocal, but partial, disruption of complex cognitive systems. Acquisition of quantitative MRI, PET studies, and neuropsychological test scores for each subject allowed us to examine the regional versus global associations with WMHI volumes.

The purpose of this study was to examine the associations between WMHI volumes, brain structure, cerebral metabolism, and cognitive performance in the absence of cerebrovascular risk factors; to use quantitative measures to assess a continuous versus a threshold effect of WMHI on brain structure and function; and to measure specific regional metabolism and cognitive domains to evaluate the possible role of frontal lobe dysfunction in subjects with WMHI.

Methods. *Subjects.* Fifty-one subjects between the ages of 19 and 91 years were selected from an ongoing longitudinal study of healthy aging at the Laboratory of Neurosciences, National Institute on Aging, National Institutes of Health. Each subject underwent rigorous medical, neurologic, and laboratory screening.[24] Subjects with chronic medical illnesses including hypertension, heart or cerebrovascular disease, psychiatric disorders, history of head trauma, or substance abuse were excluded. No subject received medication within 2 weeks of evaluation.

Quantitative MRI. MRI of the brain was performed on a 0.5-tesla imager (Picker Instruments, Cleveland, OH). Axial images were analyzed using a double-echo sequence (TR 2,000/20/80) according to previously published methods.[25,26] Eighteen 7-mm–thick contiguous sections were obtained from the foramen magnum to the vertex, parallel to an estimated orbitomeatal line. A region of interest (ROI) analysis[26] was applied to determine the volumes of the cerebral ventricles. All images were filtered to exclude radiofrequency inhomogeneities, and segmentation analysis was performed on the first echo of the double-echo sequence to determine cerebral and hemispheric CSF and brain volumes.[25] After image segmentation of brain from CSF was performed, brain matter pixels of the first echo image were added to brain matter pixels of the second echo image, and a pixel intensity histogram recalculated. The double-echo pixel intensity histogram was modeled as a gaussian distribution and pixel intensities three or more SDs above the mean were considered WMHI. All volumes were determined by counting the number of pixels identified within a given region and multiplying by the pixel voxel size (approximately 6.7 mm^3). To correct for individual differences in head size on measures of brain volume,[27] all statistical comparisons were performed on brain, CSF, and WMHI volumes calculated as a percentage of total intracranial volume. Interrater reliabilities for this method have been published.[25] WMHI volumes calculated by this method are significantly correlated ($r = 0.83$, $p < 0.001$) with operator-guided tracing techniques previously published.[11]

Neuropsychology. The Wechsler Adult Intelligence Scale (WAIS)[28] was administered to 47 of the 51 subjects to evaluate general intellectual, verbal, and visuospatial function. The Wechsler verbal and performance sums of scaled scores were used instead of IQ to avoid the confounding effect of age correction on the IQ measure. The sum of scaled scores was combined as the indicator of general intelligence.

Memory function was assessed by the Wechsler Memory Scale.[29] Frontal lobe-mediated tasks included the digit symbol subtest of the WAIS,[28] the Porteus Maze Test,[30] the FAS word list generation task,[31] and the Trail Making Test, parts A and B.[32] Raw score values for each of these neuropsychological tests were used in the analyses.

PET imaging. PET imaging was performed on a Scanditronix PC1024-7B tomograph (Uppsala, Sweden), a seven-section machine with a transverse resolution of 6 mm and an axial resolution of 10 mm. Catheters were placed in a radial artery for drawing blood samples and in an antecubital vein for injecting the isotope. Subjects were placed in the imager with their eyes covered, ears occluded, and heads held in place by a thermoplastic mask. Transmission images were obtained for attenuation correction, and then a bolus of 5 mCi of 18-fluoro-2-deoxy-D-glucose was injected intravenously. The emission imaging was begun after a 45-minute uptake period. Two interleaved images were obtained parallel to and 10 to 100 mm above the inferior orbitomeatal line, resulting in a total of 14 sections. Arterial blood samples were drawn throughout the procedure for measurement of

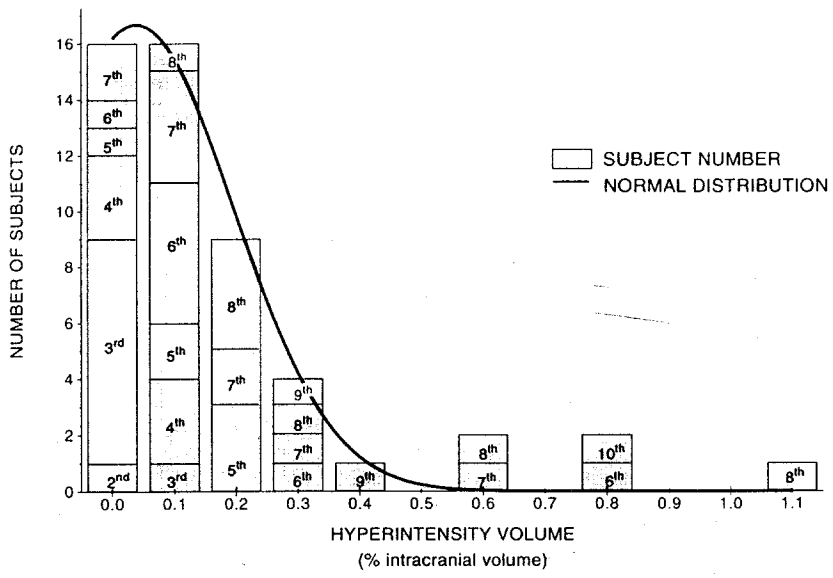

Figure 1. Distribution of white matter hyperintensity (WMHI) volumes expressed as percent of intracranial volume. Gray solid bars are total number of subjects at each interval WMHI volume. Subdivisions indicate the number of subjects by decade of age. Solid black line is a gaussian fit to the data. Ordinal numbers within vertical bar segments indicate subjects' decade of life.

plasma radioactivity and glucose concentration. Regional cerebral metabolic rates for glucose were calculated using a modification[33] of the operational equation of Sokoloff et al.[34]

PET data were analyzed using a template composed of circular ROIs that were 8 mm in diameter (48 mm^2). The ROIs were spaced evenly throughout the cortical and subcortical regions. Regional metabolic rates were obtained by averaging values in the circular regions that fell within anatomically recognized areas of the frontal, temporal, and parietal lobes.[35] Whole-brain cerebral metabolic rate of glucose was calculated by averaging regional cerebral metabolic rate of glucose from cortical and subcortical gray matter regions.

Statistics. Age-related differences were examined with Pearson correlation coefficients. Stepwise linear multiple regression was used to test the independent predictive value of WMHI volume on brain volumes, neuropsychological performance, and cerebral metabolism. Between-group comparison of patients with large WMHI volumes and age-matched controls was performed with the Wilcoxon signed rank test.

Results. *Demographics.* There were 25 women and 26 men, with a mean age of 52 ± 20 years and mean educational achievement of 16 ± 2 years. Average intelligence for the subjects was a WAIS IQ of 125 ± 12. Mean blood pressures were 124 ± 14 mm Hg systolic and 78 ± 9 mm Hg diastolic. Men had significantly more educational achievement and significantly higher mean WAIS IQ scores.

MRI measures. The volume of WMHI ranged from 0.0 to 1.1% of the intracranial volume. The distribution of subject values is displayed in figure 1. The values within each vertical bar denote the decade of life for the number of subjects indicated. Forty-six subjects had WMHI volumes between 0.0 and 0.4% of intracranial volume. WMHI values for these subjects appear normally distributed with a mean of 0.11 ± 0.10%. The remaining five subjects had volumes greater than 0.5%, which is more than three SDs from the mean of the other 46 subjects. Visual inspection of the MRIs showed that the smaller WMHI volumes were located at the genu of the frontal and occipital horns of the lateral ventricles. With increasing volume of WMHI, there was spread of hyperintense signal around the body of the lateral ventricles. In two subjects with the largest volumes of WMHI, there were small WMHI within the subcortical white matter distinct from the lateral ventricle margins. In both cases, these WMHI were in the centrum semiovale superior and lateral to the body of the lateral ventricles.

Age effects. Age-related correlations are summarized in table 1. Significant age-related differences were found for each variable except the general measure of intelligence, verbal sum of scaled scores from the WAIS, FAS scores, immediate and delayed Wechsler verbal memory scores, and diastolic blood pressure. Figure 2 displays the age-related differences in WMHI volumes. The regression slope and upper and lower 95% confidence intervals were determined for the 46 subjects with WMHI volume less than 0.5%.

Regression analyses. Stepwise linear regression was used to evaluate the independent predictive value of multiple variables in the regression model. Table 2 summarizes these findings. The amount of independent variance for each predictor variable and the total variance of the model are given for each analysis. WMHI volume was predicted using suspected risk factors[1,2,4] of age and systolic and diastolic blood pressure. Age and systolic, but not diastolic, blood pressure were significant independent predictors of WMHI volume. Since brain volumes were highly correlated with age, the association between WMHI volume, cerebral brain volume, and central CSF volume was examined in a model that included age as the other predictor variable. Both age and WMHI volume contributed sig-

Table 1. Age-related correlations

Blood pressure (47 subjects)		
Systolic	R = 0.64	$p < 0.0001$
Diastolic	R = 0.24	$p > 0.1$
Brain volumes (51 subjects)		
Cerebral volume	R = –0.59	$p < 0.0001$
Central CSF volume	R = 0.55	$p < 0.0001$
WMHI volume	R = 0.60	$p < 0.0001$
PET rCMRglc (42 subjects)		
Global gray	R = –0.59	$p < 0.0001$
Frontal	R = –0.64	$p < 0.0001$
Parietal	R = –0.61	$p < 0.0001$
Temporal	R = –0.57	$p < 0.0001$
Cognition (49 subjects)		
General IQ*	R = –0.19	$p > 0.1$
WAIS Verbal†	R = 0.23	$p > 0.1$
WAIS Performance†	R = –0.62	$p < 0.0001$
Wechsler Immediate Verbal Memory	R = –0.13	$p > 0.1$
Wechsler Delayed Verbal Memory	R = –0.23	$p > 0.1$
Wechsler Immediate Visual Memory	R = –0.41	$p < 0.01$
Wechsler Delayed Visual Memory	R = –0.46	$p < 0.001$
WAIS Digit Symbol	R = –0.69	$p < 0.0001$
Porteus Maze	R = –0.41	$p < 0.01$
FAS Word List	R = –0.02	$p > 0.1$
Trail Making, Part A	R = 0.50	$p < 0.001$
Trail Making, Part B	R = 0.55	$p < 0.001$

Blood pressure is expressed in mm Hg, cerebral volumes as percent of intracranial volume, and cerebral metabolism as mg of glucose/100 g brain/min.

WMHI White matter hyperintensity.
* Sum of verbal and performance scaled scores.
† WAIS sum of scaled score.

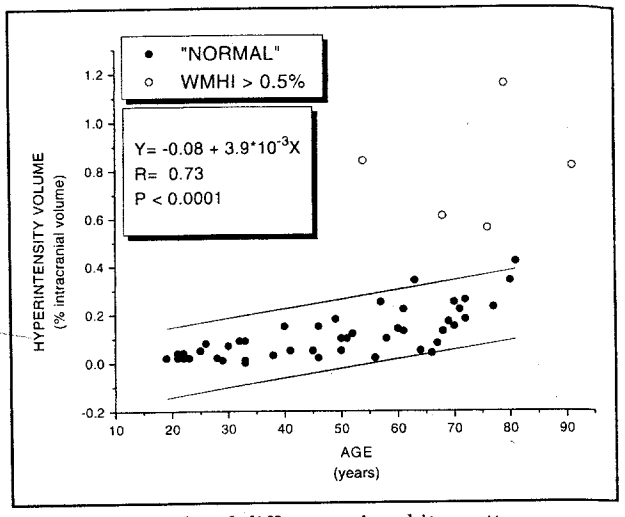

Figure 2. Age-related differences in white matter hyperintensity (WMHI) volume expressed as percent of intracranial volume. Black full circles are subjects within the 95% confidence intervals of the gaussian distribution shown in figure 1. The regression slope and statistical significance reflect these subjects. Data from subjects with WMHI volumes greater than 95% confidence limits of the gaussian distribution are plotted as open circles.

nificant independent predictive value. Age and educational achievement are both strong predictors of neuropsychological performance, and were included in the model with WMHI volumes to predict neuropsychological test scores. WMHI volume was a significant independent predictor of general intelligence scores, Wechsler immediate and delayed visual memory scores, and times on Trail Making Task A and B.

Regional cerebral glucose metabolism was predicted using age and WMHI volumes. Age explained all significant independent variance in the four PET measures of cerebral metabolism (table 1).

WMHI volume explained significant independent variance in both brain volumes and neuropsychological scores. Since it is plausible that brain volume and cerebral metabolism could also influence neuropsychological performance, another series of regression models was tested. The neuropsychological tasks where WMHI volume was a significant independent predictor were used as the dependent variables in multiple regression models that included age, educational achievement, brain volume, central CSF volume, global gray matter metabolism, and regional gray matter metabolism. All models were significant ($p < 0.01$). Educational achievement and WMHI were the significant predictors of general intelligence scores. WMHI volume and global gray matter metabolism were the significant predictors of Wechsler immediate visual memory. WMHI volume and age were the significant predictors of Wechsler delayed visual memory. WMHI remained the only significant predictor of time on Trail Making Task A, whereas WMHI and central CSF volumes were the significant predictors of time on Trail Making Task B. WMHI volumes explained greater than 40% of the variance in the Trail Making Tasks and more than 20% of the variance in the visual memory tasks. The other variables predicted no more than 10% of the variance in any model and were always entered after WMHI volume.

Threshold effect. We examined the notion of a threshold effect of WMHI volume in two ways. First, all subjects with WMHI volumes greater than 0.5% of intracranial volume were removed from analysis, and the regression analyses where WMHI was previously a significant independent predictor were repeated. After removing subjects with large WMHI volumes, the significant relations between WMHI volume, brain volume, and central CSF volumes were lost. WMHI volume, however, continued to be a significant independent predictor of general intelligence, digit symbol, immediate and delayed visual memory scores, and time on the Trail Making Task B. Systolic blood pressure also was no longer a significant predictor of WMHI volume after subjects with large WMHI volumes were removed from the analysis.

Table 2. Multiple linear regression analyses

Predicted variables	Predictor variables			Results
	WMHI volume			
	Systolic BP	Diastolic BP	Age	
WMHI	0.41‡	0.01	0.06*	0.42‡
	Brain volumes			
	Age	WMHI volume		
Cerebrum	0.35‡	0.07*		0.42‡
Central CSF	0.30‡	0.07*		0.37‡
	Neuropsychological test results			
	Age	Education	WMHI volume	
General IQ	0.02	0.10*	0.17†	0.29†
WAIS Verbal	0.04	0.27‡	0.05	0.36‡
WAIS Performance	0.29‡	0.5	0.02	0.36‡
Wechsler Immediate Verbal Memory	—	—	—	NS
Wechsler Delayed Verbal Memory	—	—	—	NS
Wechsler Immediate Visual Memory	—	—	0.29‡	0.29‡
Wechsler Delayed Visual Memory	0.04	0.04	0.25†	0.33†
WAIS Digit Symbol	0.47‡	0.02	0.04	0.54‡
Porteus Maze	0.16†	0.12†	—	0.28†
FAS Word List	—	—	—	NS
Trails A time	—	—	0.45‡	0.45‡
Trails B time	0.02	0.02	0.52‡	0.56‡

The predicted variables are shown in the left column. The amount of independent variance explained by each predictor variable of the model is shown in the middle columns. In the right column is the total variance explained by the model.

WMHI White matter hyperintensity.
BP Blood pressure.
* $p < 0.05$.
† $p < 0.01$.
‡ $p < 0.001$.

Table 3. Measures of blood pressure, brain volume, cognition, and cerebral metabolism of glucose for the five subjects with large WMHI volumes and 17 age-matched controls

	Age-matched controls	Greater than 0.5% WMHI volume
Number	17	5
Age (range)	69 ± 6 (60-81)	74 ± 14 (54-91)
WMHI*	0.19 ± 0.11	0.80 ± 0.24
Systolic BP	128 ± 11	147 ± 13§
Diastolic BP	78 ± 8	87 ± 14
Cerebrum*	79 ± 3.0	77 ± 2.0
Central CSF*	2.1 ± 0.8	3.4 ± 1.0§
General IQ†	135 ± 14	124 ± 20
WAIS Verbal‡	85 ± 9	77 ± 9
WAIS Performance‡	50 ± 9	47 ± 14
Wechsler Immediate Verbal Memory	23 ± 4	20 ± 3
Wechsler Delayed Verbal Memory	19 ± 5	17 ± 2
Wechsler Immediate Visual Memory	10 ± 2	6 ± 5§
Wechsler Delayed Visual Memory	9 ± 3	6 ± 5§
WAIS Digit Symbol	53 ± 9	46 ± 11
Porteus Maze	14 ± 3	15 ± 2
FAS Word List	46 ± 9	37 ± 8§
Trails A time (sec)	38 ± 9	66 ± 29
Trails B time (sec)	75 ± 26	153 ± 70§
Global gray matter rCMRglc	7.8 ± 0.8	6.9 ± 0.3§
Frontal lobe rCMRglc	8.4 ± 1.0	7.3 ± 0.5§
Parietal lobe rCMRglc	8.0 ± 0.9	7.2 ± 0.4
Temporal lobe rCMRglc	6.87 ± 0.9	5.99 ± 0.7

* Volume expressed as percent intracranial volume.
† IQ = verbal sum of scale scores + performance sum of scale scores.
‡ Sum of scale score (no age correction).
§ $p < 0.05$, Wilcoxon's rank sum.

In our second analysis, we examined the magnitude of the differences in our brain and neuropsychological measures for subjects with large WMHI volume by comparing the five subjects with WMHI volumes greater than 0.5% with 17 subjects matched by mean age and age range with WMHI volumes less than 0.5%. Mean values for age, blood pressure, quantitative MRI, neuropsychological scores, and PET metabolism are summarized in table 3, and individual regional cerebral metabolic rate of glucose for the global gray matter and frontal lobe metabolism are displayed in figure 3. The mean WMHI volume for subjects with large WMHI volumes was 0.8% ± 0.24% as compared with 0.19% ± 0.11% for the age-matched controls. By way of comparison to Boone et al,[11] these values correspond to a mean WMHI area of 12.9 ± 4 cm^2 (range, 10.3 to 18.9) for the five subjects with large WMHI volumes, and a mean WMHI area of 3.2 ± 1.8 cm^2 (range, 0.7 to 6.9) for the subjects with normal WMHI volumes. Subjects with large WMHI volumes had significantly higher mean systolic blood pressure (range, 134 to 167 mm Hg); significantly larger central CSF spaces; significantly lower scores on Wechsler immediate and delayed visual memory, FAS word list generation, and Trails B time; and significantly lower global gray matter and frontal lobe metabolism.

Discussion. We found that the volume of WMHI is positively associated with higher systolic blood pressure, even in subjects for whom blood pressures are in the normal range. In addition, WMHI volume was a significant independent predictor of smaller brain volumes and lower cognitive performance scores in otherwise very healthy subjects. Large WMHI volumes, defined as greater than 0.5% of intracranial volume, were present in approximately 10% of the study population, but only in those subjects greater than 50 years of age. Within this small group, the presence of large WMHI volumes was associated with significantly higher systolic blood pressure, larger central CSF volumes, lower neuropsychological test scores, and significantly lower global gray matter and frontal lobe glucose utilization.

The high frequency of large WMHI volumes in

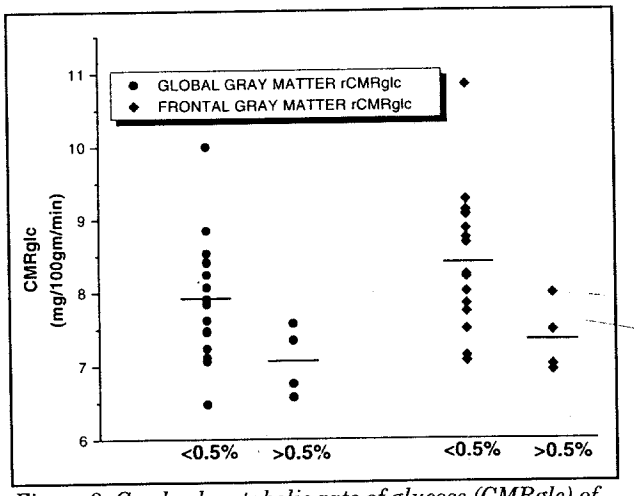

Figure 3. Cerebral metabolic rate of glucose (CMRglc) of global and frontal lobe gray matter for subjects with large white matter hyperintensity (WMHI) volumes (>0.05% of intracranial volume, x-axis) as compared with 17 age-matched controls (<0.5% of intracranial volume). Mean WMHI volumes and cerebral metabolism for the two groups are summarized in table 3.

our cohort is surprising given that our subjects were free of cerebrovascular risk factors, including hypertension. However, our finding that systolic blood pressure, even when in the normal range for age, was a significant independent predictor of WMHI volume suggests that the effect of systolic blood pressure may operate along a continuum. While this finding was present primarily in a small group of older subjects with large WMHI volumes, the impact on brain structure and function was similar to that seen in patients with well-controlled hypertension.[19,20] The significant relation between systolic blood pressure and WMHI volume is also consistent with the relation between systolic blood pressure and stroke,[36] further supporting the notion of a continuous untoward effect of blood pressure on the cerebrum. When subjects with the largest WMHI volumes were removed from the analysis, however, systolic blood pressure was no longer a significant predictor of WMHI volume. This suggests that WMHI also occur as part of the aging process independent of the effects of elevated blood pressure.[1] The frequency or impact of other causes of WMHI, however, such as cerebral amyloid angiopathy,[37-39] is unclear and was not tested directly.

For our subjects, large WMHI volumes had a disproportionate impact on systolic blood pressure, brain structure, and cerebral metabolism. When WMHI volumes were converted to area measures, the mean area of WMHI for each subject with a large WMHI volume was greater than 10 cm^2, and similar to that of Boone et al,[11] supporting the idea that a threshold size of WMHI may be necessary for clinical expression. Although present in only five subjects, large amounts of WMHI appear pathologic and may identify subjects at risk for cerebrovascular disease or further cognitive impairment. Given the small number of subjects with large WMHI volumes in our study, however, we must interpret these findings cautiously. Larger subject cohorts, and possibly longitudinal assessment, will be necessary to assess completely the untoward effects of large WMHI volumes on brain structure and function.

In agreement with previous studies,[9,11,12] we found that WMHI volume was a significant independent predictor of neuropsychological scores. Among the neuropsychological tests employed, tests of frontal lobe function were predominantly affected. These included the commonly recognized Trail Making Tasks A and B, but also the Wechsler immediate and delayed visual memory tasks. We believe the Wechsler visual memory test accesses frontal function by utilizing working memory that is located primarily in the frontal lobes.[40] That WMHI volume accounted for more variance in the immediate version of the Wechsler memory task than in the delayed version also implies that the association is between WMHI and frontal lobe working memory as opposed to temporal lobe-mediated memory function. Consistent with impaired frontal lobe function, subjects with large WMHI volumes had significantly reduced frontal lobe glucose utilization. Similar to Boone et al,[11] we noted WMHI to occur primarily adjacent to the cerebral ventricles, especially about the horns of the lateral ventricles, and occasionally extending into the centrum semiovale. Large, confluent WMHI in subcortical white matter distinct from periventricular WMHI were not seen in our subjects. Reduced frontal lobe metabolism and impaired frontal lobe neuropsychological performance indicate preferential impairment of frontal lobe neural circuitry. The long association superior-longitudinal fasciculi pass adjacent to the lateral ventricles where WMHI occur.[41] Damage to these fasciculi, especially vulnerable due to their length and proximity to WMHI, could explain the metabolic, structural, and neuropsychological consequences of WMHI.[42-44]

The relation between WMHI volume and neuropsychological test performance differed from the relation between systolic blood pressure and WMHI and the relation between WMHI, brain structure, and cerebral metabolism. The significant association between WMHI volume and neuropsychological test performance was continuous as opposed to the other relations, which were driven primarily by subjects with large WMHI volumes. The complex cognitive systems of the frontal lobes may possibly be more sensitive to the untoward effects of WMHI than the structural and metabolic effects of WMHI. Alternatively, neuropsychological tests may be more sensitive than other brain measures. This seems unlikely given that lower neuropsychological scores are not always found in association with WMHI.[13,14]

We conclude that WMHI occur even in very healthy individuals. When large (greater than 10 cm^2 or 0.5% of the intracranial volume), WMHI are associated with higher systolic blood pressure, brain atrophy, lower neuropsychological scores, and lower cere-

bral glucose utilization. WMHI may therefore explain some of the reduced brain size, cerebral metabolism, and cognitive performance in the elderly.[45-48] WMHI, by subtly affecting brain structure and function, also may make some individuals more vulnerable to the effects of late-age–onset neurodegenerative diseases, and may explain the increased prevalence of WMHI in Alzheimer's disease.[49] The association of large WMHI volumes with systolic blood pressure could also affect therapeutic decisions of antihypertensive control in the elderly, in whom isolated systolic hypertension is common.[50]

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