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The Cognitive Correlates of White Matter Abnormalities in Normal Aging: A Quantitative Review

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Cerebral white matter of asymptomatic people frequently exhibits circumscribed areas of hyperintensity on magnetic resonance (MR) images and hypodensity on computed tomography scans. However, behavioral implications of this phenomenon remain unclear. In this meta-analysis, the authors examine cumulative evidence regarding the cognitive sequelae of white matter abnormalities in adults without dementia. The influence of potential moderator variables, such as neuroimaging technique, location of the lesions, rating scale, and demographic characteristics of the sample on the association between the burden of white matter hyperintensities and cognitive performance was also examined. Results indicate that white matter abnormalities observed on MR images are associated with attenuated performance on tasks of processing speed, immediate and delayed memory, executive functions, and indices of global cognitive functioning. There was no significant link between the white matter hyperintensities and psychometric indices of intelligence or fine motor performance.

Neuroimaging studies of the state of the cerebral white matter have a relatively long history. Since introduction of magnetic resonance imaging (MRI) into clinical practice, radiologists have observed circumscribed areas of increased signal intensity in the white matter of asymptomatic individuals (Bradley, Walluch, Brant-Zawadzki, Yadley, & Wycoff, 1984). An example of such unidentified bright objects or white matter hyperintensities (WMHs) can be found in Figure 1.

Pathophysiological origins of WMH are diverse and include multiple cerebrovascular and neuropathological factors. It is likely that WMH observed on T2- and proton density-weighted MR scans represent a final common pathway of multiple events. A far-from-exhaustive list of potential sources of WMH includes a reduction in cerebral perfusion coupled with greater vulnerability of the border zones (Brant-Zawadzki, 1987), subclinical ischemia (Pantoni & Garcia, 1997), and état criblé that begins with age-related neuronal loss, results in axonal degeneration, and finally produces an extensive network of fluid-filled perivascular spaces (Ball, 1989). The most frequently observed pathological correlates of deep WMH include gliosis (Chimowitz, Estes, Furlan, & Awad, 1992; Fazekas et al., 1993), myelin pallor (Awad, Johnson, Spetzler, & Hodak, 1986; Fazekas et al., 1993), atrophy of the neuropil (Fazekas et al., 1993), and breakdown of the subependymal ventricular lining (Leifer et al., 1990; Scarpelli et al., 1994). It is of note, however, that no clear evidence of an association between WMH and cerebral blood flow has emerged to date (De Reuck et al., 1996, 1998; Fazekas, 1989; Hatazawa, Shimosegawa, Satoh, Toyoshima, & Okudera, 1997; Herholz et al., 1990; Kobari, Meyer, Ichijo, & Oravez, 1990).

In a quantitative review of clinical and demographic risk factors associated with WMH, we found that age, a history of transient ischemia attack–cerebrovascular accident (TIA–CVA), and, to a lesser extent, hypertension were robust predictors of WMH (Gunning-Dixon & Raz, 2000). Notably, diabetes, alcohol use, smoking history, and cholesterol were not associated with WMH, although it is quite possible that these conditions weigh in significantly when they reach some hypothetical threshold of severity. The observed association between WMH and age suggests that their presence may be linked to specific age-related differences in cognition.

The major goal of this review was to gauge reliability of the associations between age-related differences in the MRI appearance of the cerebral white matter and cognitive performance in nondemented adults. This review focuses on the following questions: (a) Is the presence and severity of WMH related to cognitive functioning in nondemented adults?, (b) If so, which cognitive domains are associated with WMH?, and (c) What are potential mediators of the relations between WMH and their cognitive sequelae? To examine the mediating factors, we coded the following variables: type of neuroimaging technique (computerized tomography [CT] vs. MRI), composition of participant population (i.e., healthy volunteers vs. cerebrovascular patients without dementia, male-to-female ratio), type of rating scale used (yes–no, numerical rating, volumetric quantification), topographical location (periventricular hyperintensity [PVH] vs. deep white matter hyperintensity [DWMH]), and

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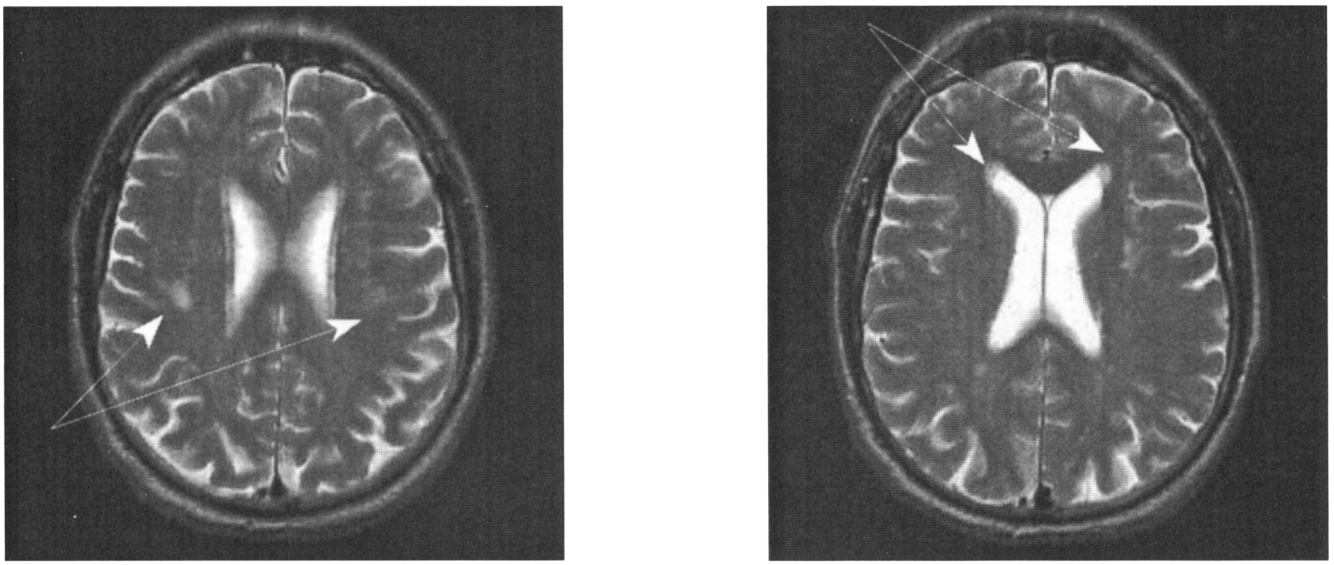

Figure 1. Examples of deep white matter hyperintensity (A) and periventricular hyperintensity (B) as they appear on axial T2-weighted magnetic resonance images. The acquisition sequence was as follows: Fast spin echo, interleaved T2- and proton-density weighted images with repetition and echo times (TR/TE) of 3300/90ef or 18ef, slice thickness 5 mm, and interslice gap 1.5 mm.

whether or not the influence of age was statistically controlled.

Method

Selection of Studies

Three procedures were used to identify studies for this quantitative review. First, we conducted a computerized search using the Medline database from 1984 through December of 1998. Key terms used to locate potential studies included *white matter lesions, leukoaraiosis,* and *white matter hyperintensities.* We examined the abstracts prior to study selection to eliminate studies that clearly did not meet the inclusion criteria outlined below. Second, we conducted a volume-by-volume search of the most recent issues (October 1998–December 1998) of potentially relevant journals to identify studies that had not yet been cited in the Medline database. These journals included *American Journal of Neuroradiology; Annals of Neurology; Archives of Neurology; Brain; European Neurology; Journal of the American Geriatrics Society; Journal of the Neurological Sciences; Journal of Neurology, Neurosurgery, and Psychiatry; Neurology; Neuroradiology; Radiology;* and *Stroke.* Finally, we inspected the bibliographies of all of the relevant articles located through the first two methods and obtained any pertinent articles that had not yet been evaluated for inclusion in the review. The search yielded 57 publications that appeared potentially acceptable for inclusion in the review.

Studies were included if they assessed the presence and severity of WMH in adults without dementia and reported relationships with cognitive abilities. To ensure that adults with dementia were not included in this review, we excluded samples that contained participants with symptoms of cognitive impairment. The studies included in the review reported obtaining extensive information about participants' health status through neurological, psychiatric, and neuropsychological evaluation. Our exclusion criteria included a diagnosis of dementia and/or descriptive phrases such as suspected dementia, memory deficits, and cognitive impairment. Studies that assessed risk factors in both adults with dementia and adults without dementia had to report results from the adults without dementia separately to be included in the review. Similarly, studies that evaluated WMH in psychiatric patients were only included in this review if data were reported separately for a normal control group. The studies had to report data sufficient to calculate Pearson's r, which was selected as the common metric for comparison of the effect sizes across studies.

Converting Effects to a Common Metric

Pearson's r was used as the common metric for the effect size across the studies. In some studies, Pearson's r was reported, whereas others contained data that could be used to calculate that index. To normalize the distribution and to make the effect sizes amenable to parametric statistical analyses, Fisher's z transformation ($z = \frac{1}{2} \log [(1 + r)/(1 - r)]$) was performed on each r. All analyses presented in this review were conducted on Fisher's z scores. The transformation has a negligible effect on the correlations that are close to zero; however, as the correlations increase in size, the transformation has a range-compressing effect. The majority of the correlations within the studies under review were small to moderate in size.

In some cases, we were unable to estimate the effect size (Pearson's r) directly from the data reported in the study. In such cases, when effect sizes were estimated from secondary information, we made assumptions about the missing information. When group differences were described as nonsignificant with no accompanying statistical values, r was considered to be 0, which in most cases amounted to a conservative estimate.

Application of the exclusion criteria yielded 23 studies, contained in 23 published articles by 21 laboratories. Participant

characteristics and study characteristics were coded to enable assessment of their respective mediating influences on WMH. The total number of participants in this meta-analysis was 4,476. Some participant characteristics are presented in Table 1.

The typical study of age-related differences in the cerebral white matter used MRI and included individuals with cerebrovascular risk factors but no history of TIA–CVA. Additionally, WMH rating scales were typically based on the number and location of the apparent lesions, and lesions were usually evaluated in the total white matter (rather than rating DWMH and PVH separately).

The studies included in this review used diverse cognitive outcome measures. The cognitive tests were classified into the following eight domains: global cognitive functioning, processing speed, executive functions, crystallized and fluid intelligence, fine motor, immediate–recent memory, and delayed memory. Participant as well as study characteristics were coded to allow assessment of their respective mediating influences on WMH.

Cognitive Domains

Tasks subsumed under the category of global functioning were those that provided an overall index of the cognitive functioning level. Global measures included the Mini-Mental State Exam (Folstein, Folstein, & McHugh, 1975) or similar screening tests of global cognitive functioning. Psychometric measures of general intellectual attitude were not included in this category.

Although processing speed is a component of many different tasks, tasks for which the primary performance criterion was response time or those that have been demonstrated to be highly dependent on processing speed were classified in the processing speed domain. The following are examples of such tasks: measures of simple and choice reaction time, Trails A of the Trail Making Test (Reitan, 1958), Stroop color and word trials (Stroop, 1935), and Digit Symbol from the Wechsler Adult Intellectual Scales—Revised (WAIS–R, Wechsler, 1981).

Tasks of executive functioning were defined as those tasks (or subtasks and subscores within more comprehensive tasks) that assessed planning, mental flexibility, and the ability to inhibit prepotent responses. Such tasks included the Wisconsin Card Sorting Test (Heaton, 1981), Category Test (booklet form, DeFilippis & McCampbell, 1979), Trail B from the Trail Making Test (Reitan, 1958), and the Stroop interference score (Stroop, 1935).

Intelligence tests were classified into measures of crystallized and fluid abilities (Horn, 1986). Vocabulary tests and the Information subtest from the WAIS–R (Wechsler, 1981) were considered indicators of crystallized abilities. Measures of reasoning abilities that involved dealing with novel stimuli or novel problems were used as indicators of fluid intelligence. Such measures included Raven's Progressive Matrices (Raven, 1960) and the Block Design subtest from the WAIS–R (Wechsler, 1981).

The motor domain was composed of the tasks in which success primarily depended on motor dexterity and coordination. Such tasks included finger tapping and the Purdue Pegboard (Tiffin & Asher, 1948).

Indices of memory were separated into immediate–recent versus delayed memory–memory consolidation domains. Immediate–recent memory tasks were defined as those tasks that required recall of material within 5 min of the initial presentation: Logical Memory, Visual Reproduction, and Paired Associated Learning from the Wechsler Memory Scale (WMS; Wechsler & Stone, 1945), and Digit Span from the WAIS–R (Wechsler, 1981). Delayed memory tasks were those that required participants to consciously remember material 30 min to 1 hr following the initial presentation of the material.

All analyses were conducted on z-transformed correlations. Positive correlations indicated that poorer cognitive performance (i.e., slower reaction time or fewer items remembered) was associated with a greater prevalence and severity of WMH.

Table 1
Descriptive Statistics of the Sample Characteristics in the Reviewed Studies

Characteristic	No. of reporting studies	*Mdn*	Range
Total (N)	23	41	13–3,301
Age (years)	23	69.15	38.6–79.1
Sex ratio (men:women)	18	0.85	0.28–3.6

Preliminary Analyses of Cognitive Correlates of WMH

The reviewed studies contained multiple indices of cognitive functioning, with more than one outcome measure per cognitive domain. If effects derived from individual outcome measures are treated as separate observations, studies with a greater number of outcome measures can exert undue influence on the inferences about the effect size. Thus, for this analysis, we retained no more than one effect per cognitive domain per study.

A more complex situation arose when analyzing the effect of covarying age and examining the relationship between location of the WMH and cognition. Multiple effect sizes obtained from the same study may not represent statistically independent observations, which can lead to underestimation of error variance and inflation of statistical significance. For example, when examining the influence of WMH location (PVH, DWMH, or total) on cognitive performance, all studies contributed only one z per location, but some studies may have contributed a z for PVH and another z for DWMH. In these types of analyses, the estimate of variability within groups would still be based on independent observations, but the estimate of variability between groups would be smaller than expected if all observations were from separate studies (see Kenny & Judd, 1986). Therefore, we performed an analysis in which the estimate of between group variability was adjusted to the appropriate degrees of freedom. Such an approach resulted in conservative inferential tests. Additionally, when evaluating the relative influence of WMH on various cognitive constructs, some studies contributed a z for only one construct whereas other studies contributed a z for multiple constructs. Again, conservative inferential tests were performed by adjusting the estimate of between group variability for the influence of nonindependence of observations.

The studies included in the analysis varied considerably in sample size. However, preliminary examination of overall relationships of WMH to cognition failed to reveal a significant link between sample size and the strength of association between cerebral and cognitive measures $r(23) = -.15$. The observed weak trend does not suggest a strong influence of publication bias in this sample. The sample size was also unrelated to error variance of WMH effects, as the squared residuals from the regression of sample size on error variance estimates showed no significant correlation with sample size, $r(23) = -.14$. Therefore, we did not weight studies according to the number of participants per study.

Results

WMH and Cognitive Performance

An overall analysis of all cognitive indices and white matter abnormalities reveals a modest association: mean Fisher's $z = 0.20$, $SD = 0.16$, $t(23) = 5.94$, $p < .001$. In general, WMH burden was associated with poor performance on cognitive tasks. In subsequent analyses, we examine the relationship between WMH and specific cognitive domains. For that purpose, correlations for each cognitive domain were submitted to independent t tests (see Table 2 for descriptive statistics). Greater WMH scores were associated with attenuated performance in global cognitive functioning, speed of processing, immediate–recent memory, delayed memory, and executive functioning. The relationship of WMH to crystallized intelligence, fluid intelligence, and fine motor functioning was not reliably different from zero. However, for all of those indices there were nonsignificant trends for WMH to be associated with attenuated performance in these domains as well.

One-way analyses of variance (ANOVAs) were performed to assess whether any of the cognitive domains related to WMH were differentially sensitive to white matter abnormalities. These analyses yielded no significant differences in the strength of the relationship between WMH and global cognitive functioning, speed of processing, immediate–recent memory, delayed memory, and executive function. However, for a more direct comparison of WMH effects across cognitive domains, we selected studies that included at least two cognitive indices. The paired sample t tests revealed that WMH are more strongly related to speed of processing than to immediate memory, $t(11) = 3.36$, $p < .01$. In addition, WMH exert a stronger influence on executive functioning than on immediate memory, $t(8) = 3.29$, $p < .05$. Also, WMH tend to be more strongly related to executive functioning than to delayed memory, $t(7) = 2.27$, $p < .08$.

In comparison of the magnitude of association between WMH and cognitive performance across diverse cognitive domains, the range of the scores may become a confounding factor. For example, restriction of range may reduce the magnitude of the observed correlations, and differential relationships between WMH and cognitive functions may reflect difference in variability rather than in the means. Because the majority of the studies did not report the range of scores, we estimated variability in the sample by computing the coefficient of variation (CV = standard deviation/mean) for each cognitive domain. Using cognitive domains as a categorical independent variable, we submitted the coefficients of variation to a one-way ANOVA. This analysis revealed that there were significant differences between the coefficients of variation associated with each cognitive domain, $F(7, 28) = 11.28$, $p < .001$. Post hoc analysis of the means indicated that the coefficients of variation associated with executive functions ($M = .56$) were larger than those of the other cognitive domains, whereas the coefficients of variation for the global domain were smaller ($M = .04$). Interestingly, despite the apparently smaller range of performance on tasks of global functioning, we observed a significant association between cognition and WMH in that domain. In contrast, the executive domain was associated with a larger range of performance but a correlation (Spearman $\rho = -.60$) between the coefficients of variation and effect size suggested that a wider range of performance on executive tasks was correlated with smaller effects. Overall, the concern that differential sensitivity of cognitive domains to WMH was overly influenced by range of performance on specific cognitive instruments was not supported. However, this analysis was conducted on only 11 of the 23 studies included in the meta-analysis because of a failure of many of the authors to report data needed to calculate coefficients of variation.

Mediating Influence of Age

We assessed the effect of age on the strength of the association between cognitive performance and WMH by conducting one-way ANOVAs for each cognitive domain. The descriptive statistics for zs, which were computed by statistically controlling for age and those in which age was not partialed out, are presented in Table 3.

Partialing out age did not have a reliable effect on the strength of the relationship between any cognitive index and WMH (all Fs < 0.1). In addition, the effects from which age had been partialed out did not differ from those in which age was not taken into account. The results of this analysis

Table 2
White Matter Hyperintensities and Cognitive Performance

Cognitive domain	No. of studies	Fisher's z ($M \pm SD$)	Mean Pearson's r
Global functioning	16	.22 ± .19***	.22
Speed	16	.22 ± .13***	.22
Immediate–recent memory	11	.12 ± .16*	.12
Delayed memory	6	.20 ± .10**	.20
Fluid intelligence	7	.09 ± .26	.09
Crystal intelligence	4	.09 ± .09	.09
Executive	9	.31 ± .26**	.30
Motor	7	.09 ± .13	.09

Note. Positive correlations indicate poorer cognitive performance associated with higher white matter hyperintensity scores.
*$p < .05$. **$p < .01$. ***$p < .001$.

Table 3
The Influence of Sample Age on the Association Between White Matter Hyperintensities and Cognitive Performance

Cognitive domain	Age not controlled (no. of studies)	Fisher's *z* (*M* ± *SD*)	Age controlled (no. of studies)	Fisher's *z* (*M* ± *SD*)
Global functioning	15	.32 ± .27	5	.16 ± .21
Speed	13	.21 ± .11	8	.24 ± .17
Immediate–recent memory	9	.11 ± .13	4	.21 ± .24
Delayed memory	6	.20 ± .09	3	.14 ± .20
Fluid intelligence	5	.14 ± .32	5	.14 ± .15
Crystal intelligence	4	.10 ± .04	2	.06 ± .23
Executive	7	.29 ± .15	5	.38 ± .32
Motor	6	.13 ± .18	4	.06 ± .09

Note. Positive correlations indicate poorer cognitive performance associated with higher white matter hyperintensity scores.

indicate that in addition to the association with age, WMH emerged as an independent predictor of cognitive functioning. Some studies reported data before and after the influence was partialed out. We analyzed the effect of statistically controlling for age on any of the relationships between WMH and cognitive performance indices, $ts < 1.50$.

Does Neuroimaging Technique Matter?

In the majority of the studies of WMH, T2-weighted MRI was the technique of choice; the rest used CT. MRI is more sensitive than CT in the detection of WMH (George et al., 1986). Therefore, one might expect that CT-based measures may yield a stronger relationship to cognitive functioning by identifying only truly pathological instances of leukoaraiosis. The analysis of the *z* scores shown in Table 4 revealed that the strength of relationship between WMH and global indices of cognitive functions did not depend on the neuroimaging technique used in a particular study: Mann–Whitney $U = 8$, $p > .12$. However, this failure to detect a significant difference in the influence of CT and MRI on WMH and global cognitive indices should be interpreted cautiously, given the very small number of CT-based studies.

Location of WMH and Cognitive Functioning

Neuropathological, clinical, and cognitive significance of spatial distribution of WMH (e.g., PVH vs. DWMH) is unclear. Because some degree of periventricular changes is considered normal, it is possible that PVHs are less likely to be associated with cognitive declines than are DWMHs. We examined this issue in two ways. First, the results of a between-study comparison revealed that location was not a significant predictor of any of the relationships between WMH and any of the cognitive indices ($Fs < 2$). The descriptive statistics relevant to this analysis are presented in Table 5.

Second, we analyzed a subsample of studies that reported data for both PVH and DWMH. Such comparison provides a more direct assessment of the relative impact of periventricular lesions and deep white matter lesions no cognitive functioning. Unfortunately, the sampled articles lacked sufficient data to enable direct comparisons for immediate and delayed memory, crystallized intelligence, and motor functioning. However, the paired *t* comparisons of PVH versus DWMH for global functioning, speed, fluid intelligence, or executive functioning, failed to yield reliable differences: all $ts < 1.2$.

Rating Scale

Because a variety of scales are used to quantify WMH, we assessed the influence of rating scale on the relationship between WMH and cognition. We hypothesized that studies that used a finer graded scale than just simple yes–no ratings would be more likely to yield a more reliable relationship between WMH and cognitive functioning. The analysis revealed that indeed, the type of rating scale was related to the strength of the association between WMH and speed of processing, $F(1, 14) = 7.60$, $p < .05$. Post hoc comparisons revealed that when WMHs were quantified using volumetric or area measurements, the WMH bore a stronger relationship to processing speed than when either presence–absence or semiquantitative scales were used to assess WMH.

Participant Characteristics

Age. The correlations between age of the sample and effects of white matter abnormalities on cognition (see Table 6) were not significant, although their magnitude ranged from small to moderate. Contrary to what one may expect, this analysis revealed that for many of the cognitive indices, samples with greater mean age showed smaller relationships between WMH and cognition. Because we studied only

Table 4
Influence of Neuroimaging Technique on the Relationship Between White Matter Hyperintensities and Global Cognitive Scales

Neuroimaging technique	No. of studies	Fisher's *z* (*M* ± *SD*)	Mean Pearson's *r*
Magnetic resonance imaging	13	.18 ± .16	.18
Computerized tomography	3	.41 ± .22	.39

Note. Positive correlations indicate poorer cognitive performance associated with higher white matter hyperintensity scores.

Table 5
The Effect of Brain Location on the Relationship Between White Matter Hyperintensity (WMH) and Cognitive Functioning

Cognitive domain	PVH		DWMH		Total WMH	
	N	Fisher's *z* (*M* ± *SD*)	*N*	Fisher's *z* (*M* ± *SD*)	*N*	Fisher's *z* (*M* ± *SD*)
Global functioning	6	.18 ± .16	4	.06 ± .15	10	.27 ± .21
Speed	3	.20 ± .13	4	.18 ± .08	11	.24 ± .17
Immediate–recent memory	1	.16	2	.17 ± .09	8	.14 ± .19
Delayed memory					7	.19 ± .11
Crystal intelligence	1	.20	1	.15	3	.06 ± .07
Fluid intelligence	2	.23 ± .06	2	.18 ± .20	3	.04 ± .29
Executive	2	.10 ± .07	3	.15 ± .19	6	.38 ± .25
Motor	1	.32	1	.15	6	.03 ± .08

Note. Positive correlations indicate poorer cognitive performance associated with higher WMH scores. PVH = periventricular hyperintensity; DWMH = deep white matter hyperintensity.

individuals without dementia, it is possible that this trend may represent a selection bias, with older individuals with WMH whom do not develop dementia being a very select group.

Sample gender composition. For the majority of the cognitive indices, the samples' sex composition showed a small to moderate influence on the domains' relationship with WMH. The larger ratio of men to women tended to be associated with larger effects of WMH on cognition although none of the correlations reached .05 significance level (see Table 6 for descriptive statistics).

Health status. Another participant variable that may have an important effect on the relationship between WMH and cognition is the health status of the participant pool. When each cognitive domain was submitted to this analysis, health status did not predict the relationship between WMH and any of the cognitive domains (all Fs < 1.3). Restriction of the range of health indicators in samples of well-screened healthy older adults could explain this finding. In addition, these data provide evidence that the relationship between WMH and cognitive functioning exists in older adults who are free of cerebrovascular risk factors such as CVA and hypertension.

Table 6
Correlations Between the Magnitude of White Matter Hyperintensity–Cognition Association and Sample Demographic Characteristics

Cognitive domain	Mean age and *z* correlation		Sex ratio (man:woman) and *z* correlation	
	N	Pearson's *r*	*N*	Pearson's *r*
Global functioning	16	.27	13	.08
Speed	16	.19	12	.11
Immediate–recent memory	11	−.04	10	.16
Delayed memory	6	.01	4	.40
Crystal intelligence	4	−.31	4	.35
Fluid intelligence	7	−.70*	6	.40
Executive	9	.46	6	.57
Motor	7	−.19	6	−.30

*$p < .05$.

Discussion

The results of this quantitative review demonstrate that the presence and extent of age-related alterations of the cerebral white matter (WMH) are related to global cognitive declines. However, certain domains of cognitive functioning—processing speed, executive functioning, and explicit (both immediate and delayed) memory—appear differentially sensitive to WMH. In contrast, we found no evidence of a reliable link between WMH on the one hand and the general indices of intelligence (crystallized or fluid) or fine motor functioning on the other hand.

With the association between WMH and cognitive performance established, the question of the mechanisms underpinning the relationship remains unclear. The pattern of cognitive deficits associated with WMH in healthy older adults resembles the one found in demyelinating diseases such as multiple sclerosis (for reviews, see Kail, 1998; Rao, 1996; Thornton & Raz, 1997). Reduction in processing speed plays a prominent role in age-associated cognitive declines (Salthouse, 1996; Verhaeghen & Salthouse, 1997). Thus, it is plausible that age-related white matter changes reflected in WMH exert their detrimental effects on cognitive functions by affecting speed of neural transmission and interneuronal connectivity, which, in turn, bring about cumulative generalized slowing, eventuating in a variety of cognitive deficits. If speed of processing is fundamental to the WMH–cognition relationship, then it is plausible that the magnitude of the observed association is proportional to the dependence of a given cognitive task on speed as a resource.

In that light, failure to detect a relationship between fluid intellectual abilities and WMH is less surprising than it seems at first glance. It is possible that this outcome is an artifact of task selection. Fluid abilities are associated with notable age-related slowing (Bors & Forrin, 1995; Fry & Hale, 1996). However, the majority of the tasks comprising the fluid intelligence domain in our review were nonspeeded. Thus, it is plausible that we would have detected a stronger relationship with WMH if more of the fluid tasks were speeded in nature. In contrast, the failure to detect a relationship between crystallized abilities and WMH is

consistent with the relative sparing of crystallized intelligence in older adults and with its relative independence of speed (Christensen et al., 1994; Wang & Kaufman, 1993).

Task selection might have affected the effects of WMH on motor performance as well. The tasks included within the motor domain were fine motor tasks executed by the upper extremities, whereas associations between WMH and motor functions may be restricted to gross motor functions such as gait disturbances, which depend on different neural systems. In addition, the reports that link WMH to gait disturbances have been primarily based on individuals with diffuse WMH and participants with dementia (e.g., Baloh, Yue, Socotch, & Jacobsen, 1995; Kerber, Enrietto, Jacobsen, & Baloh, 1998).

While considering the relations between cognitive indices and WMH, one has to keep in mind that the measures of WMH have serious methodological limitations. By design, these measures are geared to the assessment of global state of the white matter rather than local alterations thus precluding investigation of the relationship between localized cerebral circuits and cognitive operations. Furthermore, a variety of rating scales are used to assess WMH with the magnitude of the discrepancy among some of these scales being rather disconcerting (Mäntylä et al., 1997). Such discrepancy between rating scales coupled with uncertain reliability of many of the scales may have served to attenuate cognitive and WMH relationships. Finally, we only were able to make a rather crude distinction between deep white matter and periventricular lesions. Although such an analysis did not yield consistent differences in their respective correlates, it is plausible that a more precise classification of the WMH topography may yield more conclusive results.

Despite methodological limitations, the results reported here provide evidence for the influence of WMH on specific cognitive domains, particularly those that are reliant on processing speed and widely distributed neural networks. The significance of the integrity of the cerebral white matter to cognition has been documented since Geschwind and Kaplan's hallmark studies of disconnection syndromes (Geschwind & Kaplan, 1962; Geschwind, 1965a, 1965b). The appearance of WMH on neuroimaging scans allows for the further exploration of the function of the subcortical white matter. To clarify the role of WMH in cognitive aging, the impact of age-related changes in white matter integrity, directly or through their effects on basic cognitive resources (e.g., speed or working memory), must be evaluated in a multivariate framework. Such multivariate investigations call for large, well-described samples and reliable converging measures of the constructs of interest. Isolation of specific cognitive processes by design and statistical control of their interactions by analysis may aid in parsing the complex pattern of brain–behavior relationships revealed by noninvasive neuroimaging. Furthermore, measures of WMH based on more precise topographical location (e.g., frontal vs. parietal lobe) may yield more specific information regarding lesion localization and cognitive sequelae. The logistic demands of such an approach are substantial, but the rewards of clarity and understanding that they promise are just as abundant.

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