

# Cerebral White Matter Abnormalities and Lifetime Cognitive Change: A 67-Year Follow-Up of the Scottish Mental Survey of 1932

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Cerebral white matter abnormalities relate to cognitive functioning in elders. We examine whether this association is (a) independent of mental ability in youth and (b) related to general and/or specific mental abilities. We retested 83 participants of the Scottish Mental Survey of 1932 on a battery of mental tests. Their brains were scanned by magnetic resonance imaging. Three independent ratings (Fazekas) were made of periventricular, and subcortical and deep white matter abnormalities. Structural equation models showed that, irrespective of brain location, white matter abnormalities contributed about 14% of cognitive function variance in old age. Some of this effect might be due to hypertension. This contribution is independent of mental function in early life and is associated with general cognitive ability.

People who retain their cognitive functions in old age tend to have higher quality of life and live longer (Korten et al., 1999; National Research Council, 2000). Therefore, it is important to discover the factors that contribute to individual differences in

cognitive functioning among the elderly. Ideally, researchers should establish the extent to which putative determinants of differences in cognitive aging are independent of prior cognitive ability differences, but cognitive data from youth are rarely available for aging cohorts. We discovered a population-wide cohort of individuals who took a validated mental test under standardized conditions in 1932 at 11 years of age (Scottish Council for Research in Education, 1933; Deary, Whalley, Lemmon, Crawford, & Starr, 2000). A measure of early life cognitive ability was available, therefore, for many individuals who were in their late 70s at the time of this investigation.

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Follow-up studies of the Scottish Mental Survey of 1932 are a series of ongoing collaborations among the Department of Mental Health, University of Aberdeen; Departments of Psychology, Universities of Edinburgh and Aberdeen; Department of Radiology, University of Aberdeen; Department of Biophysics and Bioengineering, University of Aberdeen; Scottish Council for Research in Education; and Department of Geriatric Medicine, University of Edinburgh. The present study was supported by Grant K/MRS/50/C2785 from the Scottish Executive Health Department's Chief Scientist Office. Ian J. Deary is the recipient of a Royal Society-Wolfson Research Merit Award. Lawrence J. Whalley holds a Wellcome Trust Career Development Award. We thank Valerie Wilson and Graham Thorpe (Scottish Council for Research in Education) for providing access to Age 11 Moray House Test scores from the Scottish Mental Survey of 1932. We thank Helen Lemmon for assisting in the collection of psychometric data and John R. Crawford for advice and training on the psychometric tests. We thank John Starr for advising on the collection of medical data and radiographers Laura Frisch, Annette Lyburn, and Julie Walker for assistance with acquiring brain images.

The article is based on data collected as a part of the Scottish Mental Survey of 1932; the authors collected the present wave of data. Portions of the article, based on fewer participants, were presented at the International Congress of Psychology, July 2000, in Stockholm, Sweden. The article by Leaper et al. (2001) also reports from this database.

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In the present study, we examined the contribution of brain white matter lesions (WML) to cognitive ability differences in old age. Brain white matter abnormalities are important in the study of psychology and aging: (a) They are common, even in people with no dementia or other neurocognitive disorders; (b) they appear to be associated with other factors related to cognitive aging (such as hypertension and other illnesses, e.g., diabetes, that have an impact on vascular function); and (c) they are related to cognitive functioning in old age. In this article, we enquire whether (a) any association between WML and cognitive ability in old age is independent of cognitive ability in youth; (b) WML relate to specific or general cognitive abilities; and (c) hypertension underlies both differences in WML and cognitive function in old age.

## Brain White Matter Abnormalities

In this section, the phenomenon of brain WML is described, and causes of WML are discussed. One possible cause of both WML and cognitive aging is hypertension, which we examine in the present study.

White matter abnormalities are frequently observed on T2 weighted magnetic resonance imaging (T2W MRI) of the brain, particularly in adults over the age of 60. They are alternatively referred to as lesions or hyperintensities, which is because of their bright white appearance on T2W MRI. Among people in the

general population, the amount of these lesions increases with age between ages 60 and 90 (de Leeuw et al., 2001; Liao et al., 1997; Pantoni & Garcia, 1997). There is uncertainty concerning the clinical relevance of such abnormalities. This uncertainty is reflected in the varied nomenclature that has been applied to the lesions, including Binswanger's disease, leukoariosis, unidentified bright objects, WML (or abnormalities or hyperintensities), and periventricular lesions (PVL; or hyperintensities). There is some evidence that smooth PVL are different from patchy deep WML. Most MRI rating scales distinguish these two categories that are probably different in their pathological origins.

There is anatomical, histopathological, clinical, and experimental evidence that some white matter abnormalities are ischemic in origin (de Reuck, 1971; Erkinjuntti et al., 1996; Fazekas, Chawluk, Alavi, Hurtig, & Zimmerman, 1987; Fazekas et al., 1993; Longstreth et al., 1996; Pantoni & Garcia, 1997). Clinically, white matter disease is found most often in association with old age, arterial hypertension, diabetes mellitus, heart disease, and cardiovascular risk factors (Bots et al., 1993; Breteler, van Swieten, et al., 1994; de Leeuw et al., 2001; Liao et al., 1997). Experimental animal studies have reproduced some aspects of human WML (Pantoni & Garcia, 1997) and implicate leaks in the blood brain barrier as part of the cause of age-related cognitive decline originating from WML (Kemper, Blatt, Killiany, & Moss, 2001). Altered cerebrospinal fluid circulation might be an alternative cause of white matter abnormalities (Kimura, Tanaka, & Yoshinaga, 1992).

### White Matter Abnormalities and Cognitive Decline

This section provides an overview of the relation between WML and cognitive function in old age. The distinct contributions of WML and PVL are indicated where possible. Some studies, often including participants with and without Alzheimer's disease, reported no association between WML and cognitive decline (e.g., Harrell et al., 1991; Kertesz, Polk, & Carr, 1990; Leys et al., 1990; Starkstein et al., 1997). In more recent studies, a consensus emerged that white matter abnormalities are associated with cognitive impairment (Gupta et al., 1988; Kitagaki et al., 1997; Kuller et al., 1998; Snowden et al., 1997; Wolf, Ecker, Bettin, Dietrich, & Gertz, 2000). A quantitative review found that in healthy older people, increased WML were associated with relatively disadvantaged processing speed, memory, and executive functions (Gunning-Dixon & Raz, 2000). In the large Rotterdam Scan Study, de Groot et al. (2000; and see Breteler, van Amerongen, et al., 1994) found that WML and PVL were associated with lower performance on tests of psychomotor speed, memory, and global cognitive function. The main effect was of PVL on tasks involving speed of cognitive processing (de Groot et al., 2000). Leaper et al. (2001) reported that fluid intelligence was associated with WML but not with PVL. Hargrave, Geck, Reed, and Mungas (2000) found no relationship between the degree of psychomotor slowing and the severity of WML.

Garde, Mortensen, Krabbe, Rostrup, and Larsson (2000) found that change in Wechsler Performance IQ scores between age 50 and age 80 years correlated .32 with PVL and .28 with deep WML (people with more lesions declined more). There were significant associations, from .23 to .36, between changes in test scores from age 50 to age 80 years for Block Design and Object Assembly tests

(significantly related to both PVL and WML) and the Digit Symbol test (significantly related to PVL). Garde et al.'s (2000) study is relatively rare in possessing a measure of cognitive function that precedes, by 3 decades, the cognitive measures taken in old age.

The present study adds to these findings by asking whether WML (and PVL) relate to general mental ability or to more specific test scores in old age, after controlling for mental ability differences measured more than 6 decades previously. The next section explains why it is important to have a measure of cognitive ability that predates the development of WML. The section after that explains why it is important to ask whether WML relate to general cognitive ability or specific test scores.

### Prior Mental Ability

The correlates of mental ability in old age are multifarious, ranging from biological to social (Anstey & Christensen, 2000; Anstey & Smith, 1999). Few of these correlates are understood in a mechanistic way, and the direction of causation is often obscure. To state that—to take one debated example (Hultsch, Hertzog, Small, & Dixon, 1999)—an engaged lifestyle causes more successful cognitive aging poses various problems: It begs the question about the direction of causation between mental function and engaged lifestyle, it does not identify the ingredients in engaged lifestyles that are causal, and it does not provide a mechanism for the association between engaged lifestyle and successful cognitive aging. Thus, among the more difficult issues is separating those factors that are causes from those that are mere consequences of mental ability differences in old age. Those social, psychological, physiological, and medical factors that contribute variance to cognitive function in old age might do so wholly or partly because they correlate with mental ability differences at all ages; they might relate to life-long differences in cognitive ability rather than cognitive aging specifically (Crawford, Deary, Starr, & Whalley, 2001; Deary, 1995).

Researchers, therefore, often control for individual differences in prior cognitive ability by using test scores collected on a previous testing session, though in most studies these prior cognitive measures are themselves conducted within old age. Estimates of a person's prior mental ability may be made by using tests such as the National Adult Reading Test (Crawford et al., 2001). However, the most valuable aging cohorts are those whose participants are old and happen to have some record of mental function from youth (Plassman et al., 1995; Snowden et al., 1996). The ideal design is to have a valid measure of mental ability taken prior to the emergence of differences in the putative cognitive aging factor (e.g., WML) being assessed. This was the approach taken in the present study. Mental ability at age 11 was available to index prior ability differences. We could thus inquire whether WML contributed specifically to cognitive aging by controlling for measured prior ability.

In the present study, we examined surviving participants of the Scottish Mental Survey of 1932 (Scottish Council for Research in Education, 1933). On June 1st, 1932, almost all children resident in Scotland, born in 1921, and attending school on that day took the same mental test ( $N = 87,498$ ). The principal exceptions were a few private schools and those students absent from school because of sickness. The test was a version of Godfrey Thomson's Moray House Test No. 12 (Scottish Council for Research in

Education, 1933). It was criterion validated ( $r \approx .80$ ) against the Stanford-Binet test on a subsample of 1,000 participants of the Scottish Mental Survey of 1932. Its stability coefficient from age 11 to 77 years is .63 (disattenuated  $r = .73$ ; Deary et al., 2000). Viewing white matter abnormalities as an archaeological record of damage to the brain through adult life, we asked whether the quantity of the damage contributes some variance to mental ability differences in old age that is independent of prior ability.

### *g* in Mental Ability and Mental Aging

Studies of WML and cognition tend to report bivariate correlations between measures of white matter abnormalities and lists of cognitive tests (see the review of Gunning-Dixon & Raz, 2000). Results from psychometrics (Deary, 2001) and cognitive aging can improve on this approach. A general cognitive factor accounts for about 40–50% of the variance when a diverse mental test battery is given to a sample of the healthy population (Carroll, 1993; Deary, 2000; Spearman, 1904). Salthouse's (e.g., 1996, 2001) reviews and structural modeling showed that much of the effect of age on cognitive ability is on the general factor, with relatively little effect on specific cognitive functions. In the present study, individual differences in white matter abnormalities were hypothesized to contribute principally to differences in the general cognitive ability factor in old age.

### The Present Study

Garde et al. (2000) summed up studies between cognition and WML as follows: (a) There were too few longitudinal studies; (b) most studies were conducted over too short a period of follow-up; (c) most samples were too small; and (d) studies rarely tested community dwelling individuals, instead concentrating on highly selected samples. The present article examines the association between brain white matter abnormalities (WML and PVL) and cognitive change measured across most of the human life span (age 11 to age 78 years). It is based on the same cohort sample as the report by Leaper et al. (2001): (a) It adds a few new participants; (b) it analyzes a different combination of psychometric tests; (c) it presents entirely new analyses; and (d) it introduces the effect of medical conditions, especially hypertension. Both PVL and deep WML are rated separately. Participants are community dwelling individuals. A range of mental functions is assessed rather than merely the frequently used but insensitive Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975). The MMSE was used here as a screening test to exclude dementia. Going beyond the study by Garde et al., the following improvements to study design were adopted. White matter abnormalities (PVL and WML) were rated by three independent observers so that a latent, more reliable score could be extracted by using structural equation modeling (Bentler, 1995). Structural equation modeling was, in addition, used to construe mental test scores as a hierarchy (Carroll, 1993) so that we could discover the extent to which WML relates to changes in general cognitive function and specific mental test scores.

### Method

#### *Participants*

The study participants were 83 people (47 men, 36 women) who took part in the Scottish Mental Survey of 1932. All were born in 1921. The

present follow-up data were collected between March and December 1999 when most participants were 78 years old. Participants comprised a good spread of occupational backgrounds, as coded on highest-ever occupational status by the United Kingdom's (U.K.'s) Office of Population and Census Studies (1990) Classification of Occupations. From the least to the most skilled, the numbers of participants in the present study were as follows: unskilled II = 7; unskilled I = 7; semiskilled II = 7; semiskilled I = 4; skilled manual = 17; secretarial = 20; lesser professional = 2; professional = 10; managerial = 9. Thus, the participants were about half blue collar and half white collar workers in their past occupations. Their educational experience reflected their birth cohort in that most people (56 of the 83, 68.7%) left school by age 14 after 2 years of postprimary education. Over 95% had no full-time education after secondary school, which is again typical of the U.K. in the 1930s. Two people had university qualifications, 9 people had professional qualifications, and 11 people had other forms of postschool qualification. Participants were reasonably healthy at the time of testing and were able to attend for psychometric testing and magnetic resonance imaging. Neither occupational nor educational variables correlated significantly with brain white matter abnormalities in this group, and neither variable was included in the models.

Participants were recruited for MRI studies as follows. First, in 1997 we matched (by birth name and date of birth) the Scottish Mental Survey archive from 1932 with a local health register. In the absence of contraindications known to local family doctors (e.g., current illness or recent bereavement) and with the approval of the Local Ethics of Research Committee, we contacted 327 people chosen at random from 427 possible matches. Refusal to take any part in the study was associated with lower childhood mental ability (refusals,  $n = 52$ , mean Moray House Test score in 1932 = 32.7,  $SD = 12.8$ ; participants,  $n = 275$ , mean score in 1932 = 38.6,  $SD = 13.4$ ;  $p = .004$ ). Study procedures required cooperation with clinical examination and tests of about 3 hr in duration. Complete ascertainment was achieved for 128 participants. These 128 individuals were invited 15 months later to take part in the MRI study with repeat cognitive testing. Of these, 107 participants were seen again successfully, and complete cognitive and clinical data were obtained for a subsample of 83 participants.

None of the participants was suffering from dementia; all individuals scored 24 or better (out of a maximum of 30) on the MMSE (Folstein et al., 1975). A systematic clinical review by trained nursing staff provided details from all participants about past and present medical problems, current drug and alcohol use, and functional status. Clinical examination included respiratory function (forced expiratory volume, vital capacity), pulse, standing and lying blood pressure (average of three readings), visual acuity, and electrocardiogram. All participants were living independently in the community. None consumed more than two units of alcohol per week. Twenty-eight of the 83 people tested were drug free and without significant medical problems. Of the other 55 individuals, 40 gave a history of hypertension that was treated by antihypertensive medication in 39 participants. Twenty people gave a history of cardiovascular problems: 17 had ischemic heart disease, 8 of whom gave a history of myocardial infarction (all with a history of hypertension and 2 of whom had undergone coronary artery bypass graft surgery); 2 had an irregular heartbeat; and 1 had a congenital heart defect. Seven participants (all with a history of hypertension) reported acute episodes attributed to cerebrovascular impairment, but without lasting neurological deficit. Five people reported maturity onset diabetes controlled either by diet (2 participants) or oral hypoglycemic drugs (3 participants). Fourteen participants had survived cancer and were asymptomatic; these participants comprised prostate (4), prostate and bowel (1), bowel (1), bladder (2), breast (2), uterus (1), and skin (2).

#### *Mental Tests*

*Moray House Test.* All participants took the Moray House test (Scottish Council for Research in Education, 1933) on June 1, 1932, when they were 10.5 to 11.5 years old. It is an omnibus group-administered mental



test with 71 numbered questions (75 items in total). It has a maximum raw score of 76. It comprises the following types (and numbers) of items: following directions (14), same-opposites (11), word classification (10), analogies (8), practical (6), reasoning (5), proverbs (4), arithmetic (4), geometry (4), mixed sentences (3), ciphers (2), and other (4). Forty-five minutes were allowed for completion of the test. The test was administered in school classrooms, and teachers read a standard set of instructions. Eight practice items preceded the test. Since 1932, these data were retained by the Scottish Council for Research in Education.

For the retesting in 1999, a group of four mental tests examined different cognitive functions: nonverbal reasoning, memory and learning, processing speed, and executive function. Tests were administered on an individual basis by trained researchers in the order that follows.

**Raven's Standard Progressive Matrices.** Raven's Standard Progressive Matrices (Raven; Raven, Court, & Raven, 1977) were used as a measure of nonverbal reasoning. This test is one of the best individual tests with respect to loadings on the general cognitive ability factor (Carroll, 1993). There are 60 items organized in 5 groups of 12. Participants were allowed 20 min to complete the test. The number of correctly completed items comprised the score.

**Key Auditory Verbal Learning Test.** The Rey Auditory Verbal Learning Test (AVLT; Lezak, 1995, pp. 438–446) assessed short-term and longer term memory and learning. Participants were given 5 trials to learn a list of 15 words. They were asked to recall as many of the words as possible immediately after hearing each repetition of the list. At the conclusion of these 5 trials, a list of 15 new words was read to them. The participants were asked to recall as many of these new words as possible immediately after the list was read. Distraction was then provided by structured discussion with the tester for 5 min. Following this, participants were asked to recall as many of the original list's 15 words as possible without its being read to them again. Over the first 5 trials, recall scores rose steadily from a mean of 4.9 ( $SD = 1.7$ ) words in Trial 1 to a mean of 10.2 ( $SD = 2.8$ ) words in Trial 5. The mean words recalled from the interference list was 3.8 ( $SD = 1.6$ ), and the mean words recalled from the delayed recall of the original list was 7.8 ( $SD = 3.1$ ). Most correlations among these seven AVLT scores were high ( $r_s > .5$ ). Principal-components analysis on the scores revealed a single component (visual examination of the scree slope was used to determine the number of components) accounting for 65.7% of the total score variance. Therefore, the standardized score from this single component (the unrotated first principal component) was used as the AVLT memory score.

**Uses of Common Objects.** Lezak (1995) referred to Uses of Common Objects (Uses of Objects, p. 667) as a test of executive function or purposive action. Participants were asked to name as many uses as they could think of for a bottle, a paper clip, and a felt hat. They were allowed 90 s for each item. Before starting, participants were given several examples of different uses for a sheet of paper. They were allowed to use multiple occurrences of the objects in their suggested uses. The score was the total number of acceptable uses for all three objects.

**Digit Symbol subtest.** The Digit Symbol subtest of the Wechsler Adult Intelligence Scale—Revised (WAIS-R; Wechsler, 1981) was used as an indicator of speed of information processing (Salthouse, 1996). The test involves participants in substituting symbols for numbers according to an explicit code. It was administered as instructed in the test manual. The score was the number of correct substitutions in 90 s.

### Magnetic Resonance Imaging of the Brain

A 1.0 tesla Siemens Magnetom Impact scanner (Siemens, Bracknell, United Kingdom) was used for MRI examination of each participant's brain. A T2W fast spin-echo sequence was acquired in the axial plane with a repetition time of 4000 ms, an echo time of 96 ms, and an acquisition time of 1 min 53 s. Slice thickness was 5 mm. The gap between slices was 1.5 mm. The resulting brain images were examined for the presence of

focal and periventricular WML by three trained observers working independently (ADM, SAL, RTS; raters 1, 2, and 3, respectively). Each rater used the same semiquantitative scale to assess the severity of these lesions (Fazekas et al., 1987), hereinafter referred to as the Fazekas scale. The Fazekas scoring method produces assessments of two types of WML, each on a 4-point scale: subcortical and deep WML (Fazekas WML) and periventricular WML (Fazekas PVL). WML may range from 0 (normal appearance) to 3 (confluent lesions). PVL may take values from 0 (normal) to 3 (large, irregular areas of lesion). Fazekas total scores for each participant were obtained by adding WML and PVL scores.

### Statistical Analyses

Descriptive statistics, bivariate correlations, and principal-components analyses were performed using SPSS for Windows, Versions 9 and 10.1. Structural equation modeling was performed by using the EQS package on an Apple Macintosh computer (Bentler, 1995). Models were tested by using the maximum likelihood method.

## Results

### Correlations

Associations among the four mental tests administered at age 78 were positive, significant, and moderate to large in effect size. Pearson's  $r$  coefficients ranged from .28 to .54 (Table 1). Principal-components analysis (with examination of the scree slope used to determine the number of components) of Raven, AVLT, Uses of Objects, and Digit Symbol test scores revealed a single component accounting for 57.5% of total test score variance. The loadings of tests on this first unrotated principal component were Raven = .75, AVLT = .72, Uses of Objects = .74, and Digit Symbol test = .82. This replicates the general cognitive factor in the mental test batteries scores (Carroll, 1993; Spearman, 1904).

Interrater reliability coefficients for Fazekas WML and PVL scores are high, almost all being above .75 (Table 2, and see Leaper et al., 2001, where intrarater reliability is also high). The Fazekas total score reliability coefficients are higher: All have values greater than 0.8 (Table 1). Correlations between Fazekas WML and Fazekas PVL scores are all above .6 (Table 2), which validates the use of Fazekas total scores.

### Structural Equation Modeling

**Model structure.** Structural equation models of the data were constructed a priori by using the theoretical considerations explained in the introductory section. The four mental tests were hypothesized to share variance attributable to a general cognitive ability factor. After this latent trait was taken into account, the test scores were hypothesized to be uncorrelated (there were no correlated error terms in the models). The three ratings of the Fazekas scores were hypothesized to be indicators of true score variance. Other than that, each rater's scores were assumed to contain only occasion-specific and error variance. The latent trait from the Fazekas score was hypothesized to be a contributor to the general cognitive factor in old age, as was the IQ score at age 11. We tested the hypothesis that the Fazekas score contribution to the general cognitive factor in old age was independent of the contribution made by the prior mental ability score by initially setting the path between Fazekas score and Moray House Test score to

Table 1

*Pearson Correlations Among Ratings of Fazekas Total (Multifocal + Periventricular) Cerebral White Matter Lesion Scores and Cognitive Function Test Scores (n = 83)*

Variable	1	2	3	4	5	6	7	8
1. Fazekas total Rater 1	—							
2. Fazekas total Rater 2	.831	—						
3. Fazekas total Rater 3	.829	.842	—					
4. Raven	.309	.306	.306	—				
5. AVLT	.062	.039	.073	.277	—			
6. Digit Symbol	.261	.192	.226	.538	.514	—		
7. Uses for Objects	.255	.175	.130	.453	.409	.395	—	
8. Moray House Test of 1932	-.028	-.129	-.178	.207	.141	.298	.175	—
<i>M</i>	2.73	2.61	1.96	29.0	0.08	33.5	11.6	41.9
<i>SD</i>	1.41	1.33	1.51	8.6	1.00	10.0	4.5	10.1

*Note.* With  $n = 83$ , correlations greater than .22 have  $p$  values  $< .05$  and those greater than .28 have  $p$  values  $< .01$  (two-tailed). Raven = Raven's Standard Progressive Matrices; AVLT = Rey Auditory Verbal Learning Test.

zero in the models. A further hypothesis was that the Fazekas score contributes to general cognitive function and, when that is accounted for, there is no further association with individual mental tasks. That is, paths between the Fazekas score latent trait and individual test scores were initially fixed at zero in the models.

*Model fit.* Hypotheses implemented in the structural equation models were tested by using (a) Fazekas total scores, (b) Fazekas subcortical and deep WML (Fazekas WML), and (c) Fazekas periventricular WML (Fazekas PVL). Fit statistics for the three

basic models were good (Table 3; and see Figure 1). The chi-square was nonsignificant for all three models, and all models meet the more usual criterion that the chi-square should be less than or equal to twice the degrees of freedom. In all three models, the Bentler-Bonnet and comparative fit indices were close to or much higher than 0.9, indicating good model fit. All of the parameters included in the model made a significant contribution (their  $z$  scores were calculated by dividing the parameter estimates by their standard errors), and none was suggested for exclusion, using the Wald test. The Lagrange Multiplier test was applied to discover if there were potentially significant parameters that were omitted from the model. Those looked for especially were any association incorrectly assumed to be set at zero between (a) the Fazekas score latent trait and individual psychometric tests, and (b) childhood IQ and individual psychological tests. None of these was suggested

Table 2

*Pearson Correlations Among Ratings of Fazekas Subcortical and Deep and Periventricular White Matter Lesion (WML) Scores and Cognitive Function Test Scores (n = 83)*

Variable	Fazekas Multifocal WML			Fazekas PVL		
	1	2	3	4	5	6
1. Fazekas WML Rater 1	—					
2. Fazekas WML Rater 2	.739	—				
3. Fazekas WML Rater 3	.749	.759	—			
4. Fazekas PVL Rater 1	.669	.633	.636	—		
5. Fazekas PVL Rater 2	.717	.722	.690	.733	—	
6. Fazekas PVL Rater 3	.721	.713	.769	.737	.775	—
Raven	.306	.350	.273	.258	.209	.302
AVLT	.061	.064	.024	.053	.006	.109
Digit Symbol	.199	.258	.207	.280	.088	.217
Uses for Objects	.291	.210	.129	.173	.108	.116
Moray House Test of 1932	-.002	-.092	-.139	-.050	-.150	-.193
<i>M</i>	1.25	1.25	0.90	1.48	1.36	1.06
<i>SD</i>	0.79	0.76	0.76	0.75	0.67	0.85

*Note.* With  $n = 83$ , correlations greater than .22 have  $p$  values  $< .05$  and those greater than .28 have  $p$  values  $< .01$  (two-tailed). PVL = periventricular lesion; Raven = Raven's Standard Progressive Matrices; AVLT = Rey Auditory Verbal Learning Test.

Table 3

*Fit Statistics for Structural Equation Models of the Association Between Fazekas Scores and Cognitive Test Scores*

Variable	Fazekas		
	Total score	WML	PVL
AODASR	.065	.063	.066
Chi-square ( $df, p$ )	26.9 (19, .11)	25.0 (19, .16)	28.4 (19, .08)
Bentler-Bonnet NFI	.919	.907	.895
Bentler-Bonnet NNFI	.962	.963	.943
CFI	.974	.975	.961
Wald test <sup>a</sup>	None	None	None
Lagrange Multiplier test <sup>b</sup>	Rater 1 Fazekas vs. Moray House Test score in 1932 ( $p = .05$ )	None	Rater 2 Fazekas vs. F2 (general cognitive function; $p = .04$ )

*Note.* WML = white matter lesion; PVL = periventricular lesion; AODASR = average of the off-diagonal absolute standardized residuals; NFI = normed fit index; NNFI = nonnormed fit index; CFI = comparative fit index.

<sup>a</sup> Suggests dropping parameters. <sup>b</sup> Suggests including novel parameters.

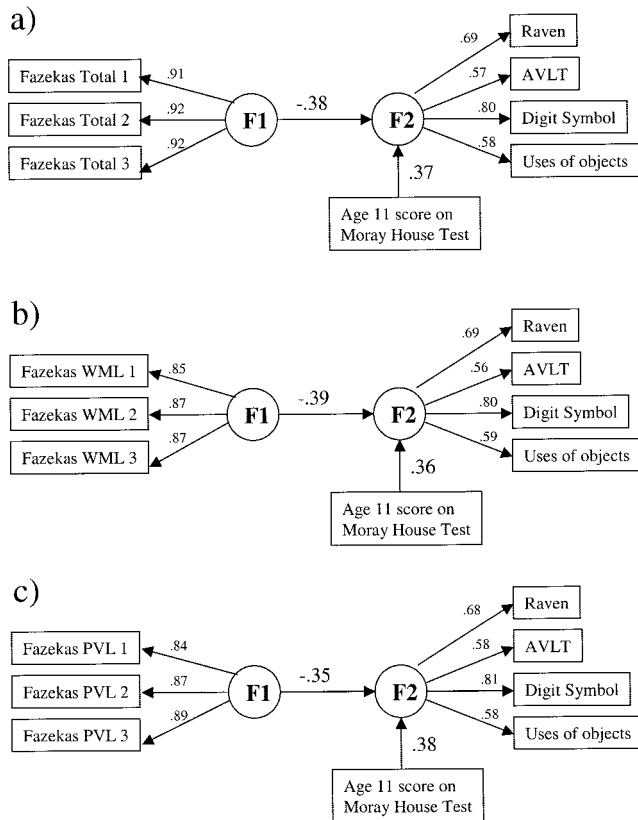


Figure 1. Structural equation model of the respective contributions to cognitive ability in old age from mental ability test scores at age 11 and (a) Fazekas total scores for cerebral white matter lesions (WML); the sum of subcortical and deep WML and periventricular lesion [PVL] scores), (b) Fazekas scores for subcortical and deep WML, and (c) Fazekas scores for periventricular WML (all  $Ns = 83$ ). For fit statistics, see Table 3. Raven = Raven's Standard Progressive Matrices; AVLT = Rey Auditory Verbal Learning Test.

for inclusion by the Lagrange Multiplier test. The only paths suggested for inclusion were between an individual rater's Fazekas score and the age 11 IQ in one model and the general cognitive factor in another, which are likely to be a Type 1 statistical error (Table 3).

**Model explanation.** All three models have similar parameter weights and identical structures (Figure 1). Therefore, a general description and explanation of the results may be applied to all of them. All three ratings of the white matter abnormalities load highly (all  $>.8$ ) on the Fazekas score latent trait. There were no significant residual intercorrelations among the three ratings. Therefore, latent trait F1 provides a measure of true score variance for the amount of white matter abnormality in participants' brains. The four mental tests load highly (all  $>.5$ ) on the general cognitive factor (F2). There were no significant residual correlations among the mental tests. This indicates that a combination of general factor and individual test-related variance was an acceptable way to construe the correlations among test scores. For the model involving Fazekas total scores (other models were similar), the contribution to the general cognitive factor variance at age 78 years was 13.7% from the IQ at 11 years of age and 14.4% from the

brain white matter abnormalities. The association between IQ at 11 years of age and Fazekas scores was not significantly greater than zero. This indicates that these two predictors are independent and, therefore, represent different causes of mental ability variance in old age.

**Models with paths from Fazekas scores to specific cognitive test scores.** After testing the initial model (see Figure 1), additional models were tested in which Fazekas scores (total, WMH and PVL) were allowed to contribute to the general latent cognitive trait and also to each individual cognitive test score in turn. The path parameters were nonsignificant for all cognitive tests for all three measures of WML (Table 4). Moreover, the chi-squares of these additional models indicate that they were not significant improvements over the models in which Fazekas scores influenced only the general cognitive trait.

**Influence of medical factors.** Recomputing the correlations in Tables 1 and 2 by omitting the 5 people with diabetes and separately omitting the 2 people with coronary artery bypass graft surgery produced trivial changes in the coefficients (details available from the authors). People with ( $n = 20$ ) and without ( $n = 63$ ) a history of cardiovascular disease did not differ in any measure of WML or cognitive function. Another extension of the basic model (Table 3 and Figure 1) was to introduce the presence ( $n = 40$ ) or absence ( $n = 43$ ) of a history of hypertension as a putative contributor to WML and cognitive function (Table 5 and Figure 2). These models fit well (Table 5). Hypertension accounts for significant variance to WML scores and to general cognitive scores in old age (Figure 2). The variance contributed to cognitive function is both direct and mediated through WML scores. Hypertension was not associated with IQ at age 11.

## Discussion

The novel finding here is that the amount of brain white matter abnormalities makes a significant contribution, independent of childhood mental ability differences, to general cognitive ability

Table 4

Statistics for Additional Structural Equation Models in Which Fazekas Scores Are Allowed to Influence Single Specific Cognitive Test Scores in Addition to General Cognitive Function

Pathway added from Fazekas score to	Fazekas		
	Total score	WML	PVL
Raven			
Path parameter ( $p$ )	.16 (.10)	.18 (.09)	.15 (.15)
Chi-square	24.2	22.1	26.3
AVLT			
Path parameter ( $p$ )	-.17 (.14)	-.20 (.09)	-.13 (.27)
Chi-square	24.5	21.9	27.1
Digit Symbol			
Path parameter ( $p$ )	-.05 (.65)	-.07 (.56)	-.04 (.75)
Chi-square	26.7	24.6	28.3
Uses of Objects			
Path parameter ( $p$ )	.01 (.91)	.05 (.69)	-.02 (.84)
Chi-square	26.9	24.8	28.4

Note. WML = white matter lesion; PVL = periventricular lesion; Raven = Raven's Standard Progressive Matrices; AVLT = Auditory Verbal Learning Test. All models have 18  $dfs$ .

Table 5  
Fit Statistics for Structural Equation Models of the Association  
Between Fazekas Scores, Hypertension, and Cognitive Test  
Scores

Variable	Fazekas		
	Total score	WML	PVL
AODASR	.067	.065	.068
Chi-square ( <i>df</i> , <i>p</i> )	41.5 (25, .02)	37.4 (25, .05)	42.6 (25, .02)
Bentler–Bonnet NFI	.883	.871	.854
Bentler–Bonnet NNFI	.926	.929	.901
CFI	.948	.951	.931
Wald test <sup>a</sup>	None	None	None
Lagrange Multiplier test <sup>b</sup>	Rater 1 Fazekas vs. Moray House Test score in 1932 ( <i>p</i> = .04)	None	Rater 2 Fazekas vs. F2 (general cognitive function; <i>p</i> = .04)

Note. WML = white matter lesion; PVL = periventricular lesion; AODASR = average of the off-diagonal absolute standardized residuals; NFI = normed fit index; NNFI = nonnormed fit index; CFI = comparative fit index.

<sup>a</sup> Suggests dropping parameters. <sup>b</sup> Suggests including novel parameters.

differences in old age. In addition, there was an indication that hypertension might in part account for the effect of WML on cognition in old age and additionally have a small direct effect (Deary, Starr, & MacLennan, 1998).

With regard to studies of white matter abnormalities and age-related cognitive change, the present study extends the follow-up period used to assess cognitive change from 30 years in the study by Garde et al. (2000) to 67 years. The results of our study are remarkably similar. In the Garde et al. study, the strongest correlation between white matter hyperintensities and age-related cognitive change was .36, which is similar in weight to the parameter here that links the Fazekas scores to the general cognitive factor at age 78. Therefore, for community dwelling individuals at about age 80, white matter hyperintensities in the brain account for about 14% of the variance in cognitive function. This substantial contribution is independent of ability scores obtained in youth.

The data here encourage two lines of further research. First, here and more strongly elsewhere (Deary et al., 2000), we show that the causes of individual differences in mental ability at 11 years of age persist until the late 70s. Therefore the search for the causes of intelligence differences in youth is relevant to research on aging because much variance from youth persists into old age. Second, we report that a separate contribution is made by white matter abnormalities; therefore, avoiding risk factors for WML or preventing their accumulation may ameliorate age-related cognitive decrements (Gorelick, 1999). Monozygotic twins reared together were tested for cardiovascular risk factors at a mean age of 48 years, and their brains were scanned at 73 years of age. Those twins with higher blood pressure, poorer glucose tolerance, and higher HDL cholesterol at midlife had more white matter hyperintensities in old age (Carmelli et al., 1999). These risk factors were associated with between cotwin differences in WML, indi-

cating that they originated from neither genetic nor shared family effects, and they were not merely related to age differences. Longitudinal research in the large Epidemiology of Vascular Aging study showed that people with hypertension had more WML and those people whose blood pressure was controlled with anti-hypertensives developed fewer WML (Dufouil et al., 2001). Thus, research on the etiology and pathogenesis of brain WML is relevant to cognitive aging because physiological and medical factors, such as hypertension and diabetes, that contribute to their accumulation also affect mental ability in middle age and old age (Deary, 1998; Fontbonne, Berr, Ducimetiere, & Alperovitch, 2001; Knopman et al., 2001; Starr, 1999; Waldstein, Manuck, Ryan, & Muldoon, 1991). The understanding of the functional neurobiology of brain aging will be enhanced by the discovery of interactions among etiological factors. For example, WML might have an especially severe impact on cognitive aging in the presence of the  $\epsilon 4$  allele of the gene for apolipoprotein E (Carmelli et al., 2000).

Some argue that subcortical WML disrupt short corticocortical fibers, whereas PVL may reflect damage to areas with closely packed long association fibers connecting distant cortical areas (de

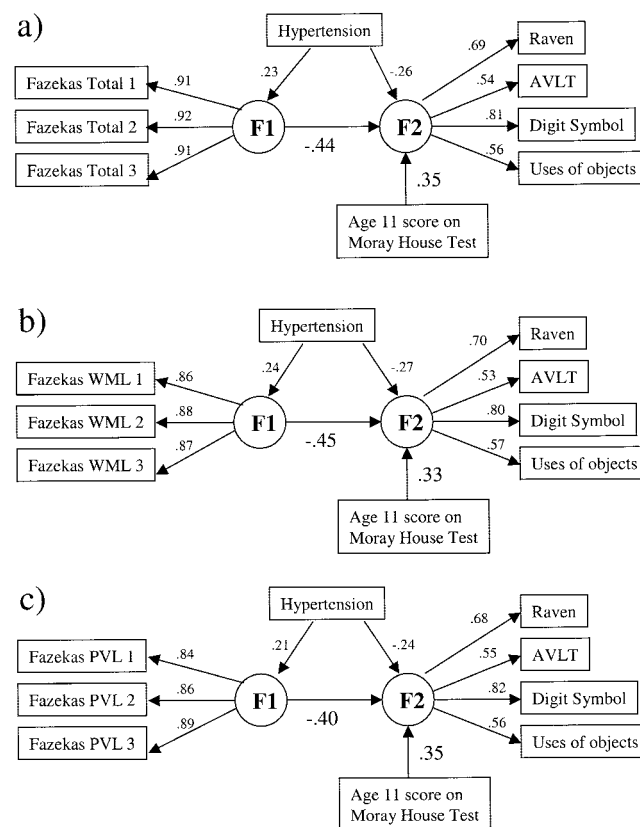


Figure 2. Structural equation model of the respective contributions to cognitive ability in old age from mental ability test scores at age 11, hypertension, and (a) Fazekas total scores for cerebral white matter lesions (WML; the sum of subcortical and deep WML and periventricular lesion [PVL] scores), (b) Fazekas scores for subcortical and deep WML, and (c) Fazekas scores for periventricular WML (all *Ns* = 83). For fit statistics, see Table 5. Raven = Raven's Standard Progressive Matrices; AVL T = Rey Auditory Verbal Learning Test.



Groot et al., 2000). According to the hypothesis that white matter abnormalities cause a disconnection syndrome (Mesulam, 1990; Wolfe, Linn, Babikian, Knoefel, & Albert, 1990), WML are likely to disrupt local networks while PVL are more likely to impair cognitive functions that require coordination of multiple distant cortical areas. The evidence that the pathogenesis of WML and PVL is different (Fazekas et al., 1993) and the different cognitive associations of ventricular enlargement and WML (Breteler, van Amerongen, et al., 1994) suggest that ventricular enlargement and PVL may both reflect a disturbance of cerebrospinal fluid circulation and/or cortical atrophy. Future research should examine the extent of WML in different anatomical locations, PVL, ventricular enlargement, and atrophy of both grey and white matter further to clarify their association with impairment of specific cognitive domains.

In conclusion, the strengths of the present study are (a) the unusual availability of valid prior mental ability scores from youth, (b) the multiple assessments of WML in the same participants, and (c) a structural equation model approach that allows partitioning of effects to general cognitive ability and specific cognitive test scores. The results suggest that WML, in general, whether the lesions be periventricular or subcortical and deep, contribute to variance in general cognitive ability rather than to the specific abilities tested here. Two cautions are necessary. First, the number of participants in the present study is modest. Nevertheless, the present study had 80% power to detect an association of .3 between IQ at age 11 and Fazekas scores (with  $\alpha$  set at .05, two-tailed). Therefore, it may be assumed that the contributions of mental ability in youth and white matter abnormalities are relatively independent. Second, one caution about stating that the contribution of our predictors is to general cognitive function is the adequacy of the mental test battery. Though we chose single test markers for 4 separate types of ability, the scores derived from the tests did have multiple indicators. The Raven test comprises 5 sets of 12 items, the AVLT test has several administrations, and the Uses of Objects test has 3 separate presentations. It would be surprising, therefore, if the 4 tests between them did not afford an adequate general factor to be extracted. A related caution is that there was no attempt made to examine the precise locations or volumes of WML or PVL, for example, whether these were frontal, parietal, and temporal, and whether this might have any correlation with specific cognitive domains (e.g., see de Carli et al., 1995).

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