NEUROLOGY

White matter integrity and cognition in childhood and old age

I. J. Deary, M. E. Bastin, A. Pattie, J. D. Clayden, L. J. Whalley, J. M. Starr and J. M. Wardlaw

Neurology 2006;66;505-512
DOI: 10.1212/01.wnl.0000199954.81900.e2

White matter integrity and cognition in childhood and old age

I.J. Deary, PhD*; M.E. Bastin, DPhil*; A. Pattie, BSc; J.D. Clayden, MSc; L.J. Whalley, MD; J.M. Starr, MD; and J.M Wardlaw, MD

Abstract—*Objective:* To test the hypothesis that white matter integrity, as measured by diffusion tensor and magnetization transfer MRI is significantly associated with cognitive ability measured in youth and old age. *Methods:* Forty, nondemented, surviving participants of the Scottish Mental Survey of 1932 underwent brain MRI and a battery of psychometric tests covering major cognitive domains and tests of information processing efficiency. IQ scores were available from age 11. Mean diffusivity, fractional anisotropy (FA), and magnetization transfer ratio (MTR) were measured in frontal and parieto-occipital white matter and centrum semiovale. *Results:* Centrum semiovale FA correlated (r = 0.36 to 0.56; $p < 0.02$) with contemporaneous (age 83) scores on psychometric tests of nonverbal reasoning, working memory, executive function, and information processing efficiency. Centrum semiovale FA also correlated with IQ at age 11 ($r = 0.37$; $p = 0.02$). Controlling for IQ at age 11 and information processing at age 83 attenuated the association between centrum semiovale FA and general cognitive ability by approximately 85%. MTR, largely, did not show significant correlations with cognitive test scores. *Conclusions:* These data support the information processing efficiency hypothesis of cognitive aging and suggest one foundation for individual differences in processing efficiency. They also suggest that studies of imaging and cognition in the elderly should take into account prior mental ability rather than assuming that any associations between imaging parameters and cognitive test scores are the result of age-related changes.

NEUROLOGY 2006;66:505–512

The "usual" age-related decline in some cognitive domains has been attributed partly to age-related decreases in the efficiency of information processing.[1-5] What is missing from this research is a mechanistic understanding of cognitive aging and information processing efficiency in terms of the brain's biology.[2,6] To work efficiently, complex cognitive functions require intact connections between distant brain regions that form neural networks.[7] Retaining the integrity of the brain's white matter might be important for minimizing the detrimental effects of aging on cognition.[8]

Diffusion tensor (DT) MRI provides age-sensitive indicators of the state of the cerebral white matter: mean diffusivity (<D>) and fractional anisotropy (FA).[9,10] <D> and FA correlate significantly with cognitive ability in old age,[11,12] especially with executive function.[13] These studies provide some evidence for disruption of white matter tracts, so-called cortical "disconnection," as a mechanism for age-related cognitive decline.[11] To date, however, DT-MRI cognition studies have included only relatively few subjects and used a limited range of cognitive tests, which did not assess some major domains. Crucially, none has adequately assessed efficiency of information processing, a linking construct between white matter indexes and higher-level cognitive test scores.[6,14]

Magnetization transfer (MT) MRI might also contribute to understanding the biologic basis of cognitive aging, as it has with other disorders.[15-17] Studies of MT-MRI and cognition in healthy people older than the seventh decade are overdue.[18]

Here, we test the hypotheses that white matter integrity in old age, as measured by DT-MRI and MT-MRI, is related to 1) cognitive ability in youth; 2) cognitive ability in old age, especially executive function; and 3) the efficiency of information processing and whether this can substantially account for the associations between imaging parameters and cognitive test scores.

Methods. *Subjects.* Subjects were surviving participants of the Scottish Mental Survey of 1932 (SMS1932).[19] All were born in

Editorial, see page 470

*These authors contributed equally to this work.

From the Department of Psychology (I.J.D., A.P.), School of Philosophy, Psychology, and Language Sciences, Department of Medical and Radiological Sciences (Medical Physics) (M.E.B.), School of Clinical Sciences and Community Health, Doctoral Training Centre (J.D.C.), Neuroinformatics, School of Informatics, Department of Geriatric Medicine (J.M.S.), and Department of Clinical Neurosciences (J.M.W.), School of Molecular and Clinical Medicine, University of Edinburgh, and Department of Mental Health (L.J.W.), University of Aberdeen, UK.

Ian Deary is the recipient of a Royal Society–Wolfson Research Merit Award, which also funded the collection of phenotypic data for this study.

Disclosure: The authors report no conflicts of interest.

Received April 20, 2005. Accepted in final form December 2, 2005.

Address correspondence and reprint requests to Dr. I.J. Deary, Psychology, University of Edinburgh, 7 George Square, Edinburgh, EH8 9JZ, UK; e-mail: I.Deary@ed.ac.uk. Address correspondence concerning technical aspects of imaging to Dr. M.E. Bastin; e-mail: Mark.Bastin@ed.ac.uk

1921 and were living independently in the community. They took part, as members of the Lothian Birth Cohort 1921 (LBC1921), in a follow-up of the SMS1932 between 1999 and 2001 at a mean age of 79 years.[20] A further follow-up of cognitive testing took place during 2004 at a mean age of 83 years. During that follow-up, the subjects were invited to undergo MRI of the brain. There were no selection criteria; subjects were invited to undergo MRI as they appeared for follow-up.

Cognitive and information processing tests. Subjects undertook the battery of cognitive tests described below. The Moray House Test was taken on June 1, 1932, at about 11 years, with all other tests being administered during 2004 at age 83.

Prior ability and dementia screen tests. The Moray House Test[19,20] is a group-administered test with a 45-minute time limit. It has a maximum score of 76. It contains many verbal reasoning items and also some numerical, spatial, and abstract reasoning items. It was corrected for age (in days) at the time of testing and converted to an IQ-type score (mean = 100; SD = 15).

The National Adult Reading Test[21] provides an estimate of prior ability. It involves reading 50 words that do not follow the normal rules of pronunciation or stress.

The Mini-Mental State Examination (MMSE)[22] is used as a brief screening test for dementia. It has a maximum score of 30.

Assessments of current cognitive ability. The Digit Symbol[23] is a subtest of the Wechsler Adult Intelligence Scale–III (UK). It is used to provide information about the efficiency of information processing. It involves entering symbols as quickly as possible according to a given code.

Letter–Number Sequencing[23] is also a subtest of the Wechsler Adult Intelligence Scale–III. It is used to assess efficiency of working memory. It involves listening to jumbled sequences of letters and numbers and recounting them with the numbers first in numerical order, followed by the letters in alphabetical order.

Verbal Fluency[24] is used to assess executive function. It involves stating as many words as possible in 1 minute that begin with a given letter. The letters used were C, F, and L.

Raven Standard Progressive Matrices[25] is used to assess nonverbal reasoning. It was used with a 20-minute time limit. The test involves inspecting logically constructed abstract designs, each with a piece missing. The task is to select the correct missing piece from a number of answer options.

Logical Memory[26] is from the Wechsler Memory Scale–Revised. Participants are read aloud a short story (A) containing 25 memory items. Immediately after this, the participant recalls as much of the story as possible. The process is repeated with a second story (B). After a minimum of 30 minutes' delay, participants recall as much as they can about each story. Because the immediate and delayed recall scores were highly correlated (r = 0.79 and 0.81 for stories A and B), they were summed to form a single score that could range from 0 to 100.

Information processing tests. The following tests are at a different level of reduction than standard psychometric tests. The former use complex stimuli and assess high-level cognitive abilities. Information processing tests use tightly controlled stimulus–response contingencies and timings and assess fundamental parameters of information processing.[14] They are used as intermediate phenotypes (sometimes called endophenotypes), between high-level cognitive test scores and aspects of brain structure and function.

Reaction time used a self-contained reaction time device. It was described in detail and illustrated previously.[27] The following measures were obtained: simple reaction time mean and SD; and choice reaction time mean and SD. There were 20 and 40 test trials for the simple and choice reaction time tests with eight practice items each. The interstimulus interval varied randomly between 1 and 3 seconds.

Inspection time is a two-alternative, forced-choice psychophysical test of the efficiency of the early stages of visual information processing. It does not involve any speeded physical response. The test used was described in detail and illustrated previously.[28] Subjects observed a stimulus composed of two parallel vertical lines of markedly different lengths. The task was to state whether the long line was on the right or the left. The stimuli were backward masked after exposure. The stimulus durations took 15 values from 6.25 to 250 milliseconds. There were 10 trials at each duration, with 150 trials in total. The stimuli were presented randomly with respect to duration and the position of the long line (right or left). The total number of correct trials was used as the score.

MRI protocol. All MRI data were obtained using a GE Signa LX 1.5 T (General Electric, Milwaukee, WI) clinical scanner equipped with a self-shielding gradient set (22 mT/m maximum gradient strength) and manufacturer-supplied "birdcage" quadrature head coil. The MRI examination consisted of a standard fast spin-echo (FSE) T2-weighted sequence, a fluid-attenuated inversion recovery (FLAIR) T2-weighted FSE sequence, and MT-MRI and DT-MRI protocols. Twenty-eight contiguous axial slice locations with a field of view (FOV) of 240 × 240 mm and thickness 5 mm were imaged using the T2-weighted FSE sequence. All subsequent sequences shared these contiguous slice locations, FOV, and slice thickness. The duration of the examination was approximately 30 minutes.

The MT-MRI protocol consisted of two standard SE sequences: one with a MT saturation pulse and one without. The MT pulse was a single sinc-shaped pulse of duration 16 milliseconds and peak amplitude 1.3 times higher than that of the 90º pulse applied 1 kHz from the water resonance. The acquisition parameters for these SE sequences, which in the absence of the MT pulse generate essentially proton density contrast, were an imaging matrix of 256 × 128, a repetition time (TR) of 1,730 milliseconds, and an echo time (TE) of 20 milliseconds.[29]

In the DT-MRI protocol, diffusion-weighted images were acquired using a single-shot spin-echo echo-planar (EP) imaging sequence. Sets of axial EP images (b = 0 and 1,000 s/mm^2) were collected with diffusion gradients applied sequentially along six noncollinear directions.[30] Five acquisitions were collected per slice position. The acquisition parameters were an acquisition matrix of 128 × 128 (zero filled to 256 × 256), a TR of 8 seconds, and a TE of 97.4 milliseconds.

Image processing. All DICOM format magnitude images were transferred from the scanner to a Sun Blade 2000 workstation (Sun Microsystems, Mountain View, CA) and converted into Analyze (Mayo Foundation, Rochester, MN) format.

Maps of the magnetization transfer ratio (MTR) were generated in the following manner. First, the SE imaging data collected with the MT pulse were registered to the SE images collected without the saturation pulse (proton density images) using FLIRT (www.fmrib.ox.ac.uk/fsl), a three-dimensional computational image alignment program.[31] Second, the MTR was calculated on a voxel-by-voxel basis using the following formula: $MTR = 100([M_0 - M_s]/M_0)$, where M_s and M_0 represent signal intensities with and without the saturation pulse.[29] Finally, the T2-weighed FSE and FLAIR T2-weighted FSE images were registered to the proton density SE images, so that regions of interest (ROIs) could be drawn on these structural images and transferred to the MTR maps.

With use of FLIRT, bulk patient motion and eddy current–induced artifacts were removed from the DT-MRI data by registering the diffusion-weighted to the T2-weighted imaging volumes. From these MRI data, the apparent diffusion tensor of water (**D**) was calculated in each voxel from the signal intensities in the component EP images.[32] Maps of <D> and FA for every patient were generated on a voxel-by-voxel basis from the sorted eigen values of D and converted into Analyze format.[9]

ROI analysis. In each subject, values of <D>, FA, and MTR were obtained for normal-appearing frontal and parieto-occipital periventricular white matter and centrum semiovale using the following method (figures 1 and 2). So that the observer was not influenced by values of <D>, FA, or MTR, all ROIs were defined on the T2-weighted FSE images. With use of the co-registered T2-weighted FSE and FLAIR T2-weighted FSE images to avoid areas of signal hyperintensity as much as possible, multiple small square (25 voxels, volume 110 mm^3) ROIs were placed in normal-appearing white matter near the anterior and posterior horns of the lateral ventricles and in centrum semiovale on the MTR maps. Partial volume effects were minimized by positioning the ROI at least 3 voxels from both the edge of the ventricles and abnormally appearing white matter. After values of MTR were obtained from these regions, the ROIs were transferred to the T2-weighted EP images collected in the DT-MRI experiment. As the T2-weighted EP images and the DT-MRI parametric maps were by definition co-registered, this allowed <D> and FA to be measured simultaneously in each ROI. Finally, mean <D>, FA, and MTR were calculated for frontal and parieto-occipital white matter and cen-

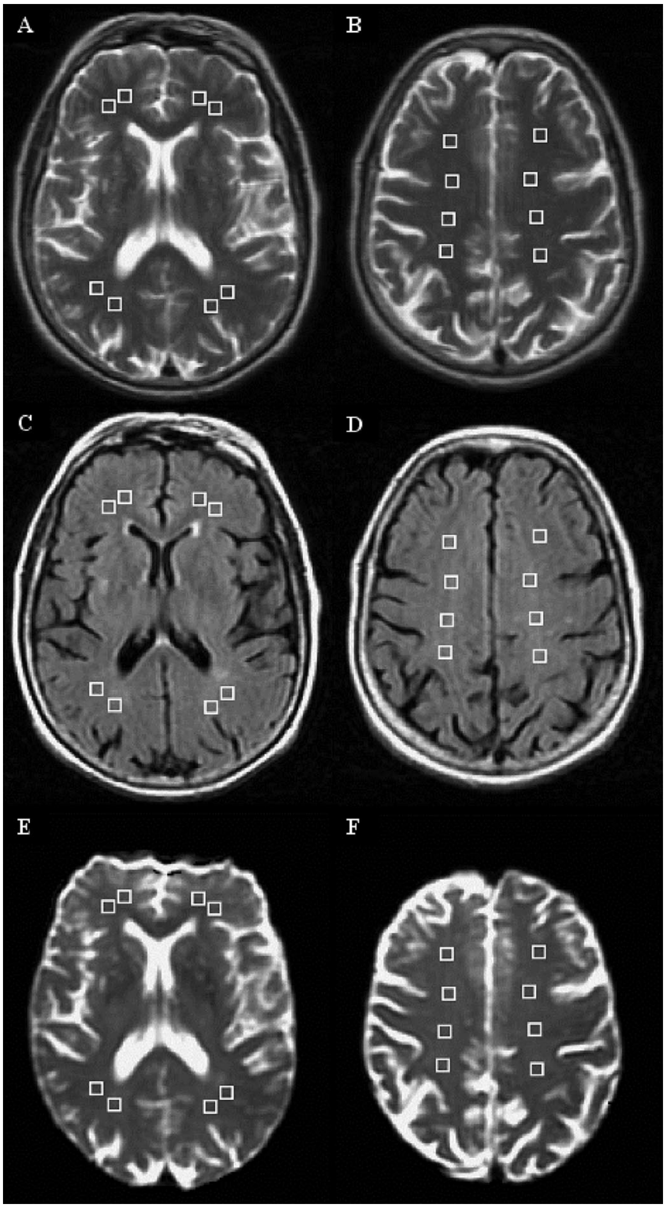

Figure 1. An example of the placement of small square regions of interest in normal-appearing frontal and parieto-occipital periventricular white matter and centrum semiovale: T2-weighted fast spin echo (FSE) (A,B), fluid-attenuated inversion recovery T2-weighted FSE (C, D), and T2-weighted echo planar images (E, F) acquired from an 83-year-old woman.

trum semiovale from the average of the left and right hemisphere values for each region in every subject. The observer was blind to the clinical status and cognitive function of participants.

Statistical analysis. Pearson correlation coefficient was used to test the associations between DT-MRI and MT-MRI parameters and cognitive test scores. There were no significant sex differences in any cognitive test or in any of the DT-MRI and MT-MRI parameters; therefore, the two sexes were analyzed together. The issue of multiple statistical testing must be addressed. There are three quantitative MRI parameters (<D>, FA, and MTR) in three brain regions, each correlated with 14 cognitive variables. The cognitive variables, especially, are not independent, making a Bonferroni-type correction inappropriate. Nevertheless, it is clear that results are likely to be due to chance if a p value of 0.05 is used to indicate significance. The prudent approach here is to acknowledge that very low p values are more likely to indicate replicable associations (we pay special attention to p values less than 0.01), to examine for consistency of correlations within one brain region, and to compare them with previous findings for replicability.

A measure of general cognitive ability was created from the tests of current cognitive function at age 83 (Raven Matrices, Digit Symbol, Letter–Number Sequencing, Logical Memory, and Verbal Fluency). This was done by subjecting these five tests to principal components analysis. Scree slope analysis and the eigenvalues-greater-than-1 rule both indicated that there was a single component accounting for 60.1% of the total variance. Scores on this first unrotated principal component were saved as standardized scores (mean = 0, SD = 1).

Path analysis, performed using the EQS structural equation modeling package (Multivariate Software, Encino, CA), was used to test a theoretical model of the web of associations between a number of key variables. Crucially, here, we were interested in testing whether the bivariate association between white matter integrity and cognitive ability at age 83 was mediated via information processing efficiency. The path analysis tested the model (figure 3 shows the structure of the model; the numbers may be ignored at this stage) that the influence of white matter connectivity, assessed with DT-MRI, on cognitive test scores in old age is accounted for by 1) the association between white matter integrity and childhood IQ and 2) via the mediating influence of efficiency of information processing. Simple reaction time SD was chosen here as it had the strongest association with cognitive test scores, but similar findings were obtained when the other reaction time parameters were used in alternative models. Notice that there are only four paths in the model, whereas with four measured variables, there are six possible bivariate associations in the covariance matrix. Therefore, the path analysis essentially tested whether these six associations can be accounted for by just four paths, giving the model economy. Unidirectional arrows in the model represent putative causal pathways, whereas the bidirectional arrow denotes a correlation without imputed causation. Fit of the model was tested using a number of standard indexes, described in Results. The strength of association between adjacent variables in the model is expressed as parameter weights. The numbers alongside the model's arrows may be thought of as standardized partial beta weights; if squared, they represent the variance shared by adjacent variables.

Results. Seventy-one LBC1921 subjects were invited to participate in the MRI study. Of these volunteers, 16 did not wish to have an MRI scan, 5 agreed but then later cancelled appointments (4 were unwell and 1 changed their mind about participating in the study), 3 had claustrophobia, 1 had a pacemaker, 1 had dizziness when lying flat, 1 was unable to lie in a supine position due to kyphosis of the upper spine, and 1 did not complete the full examination. This resulted in 43 DT-MRI and MT-MRI data sets. One subject was then found to have a meningioma on structural MRI, and two had such extensive regions of signal abnormality in white matter on T2-weighted MRI that it was not possible to place ROIs in normal-appearing tissue. After these 3 subjects were excluded, 40 subjects (21 men, 19 women) with complete MRI and cognitive data were included in the analyses. All subjects had MMSE scores of 24 or greater, and none had a history of dementia.

By comparison with the total of 288 LBC1921 subjects who were tested in this wave, these 40 subjects were similar on childhood ability Moray House Test raw scores (imaging sample mean = 48.4, SD = 12.2; whole sample mean = 46.2, SD = 12.1) and on MMSE scores at age 83 (imaging sample mean = 28.4, SD = 1.7; whole sample mean = 28.0, SD = 2.0). One subject included in this report took part in a previous imaging study.[12] However, the cognitive and imaging data used here are new.

MRI results. Table 1 shows <D>, FA, and MTR values for frontal, parieto-occipital, and centrum semiovale regions. There were differences between the three regions

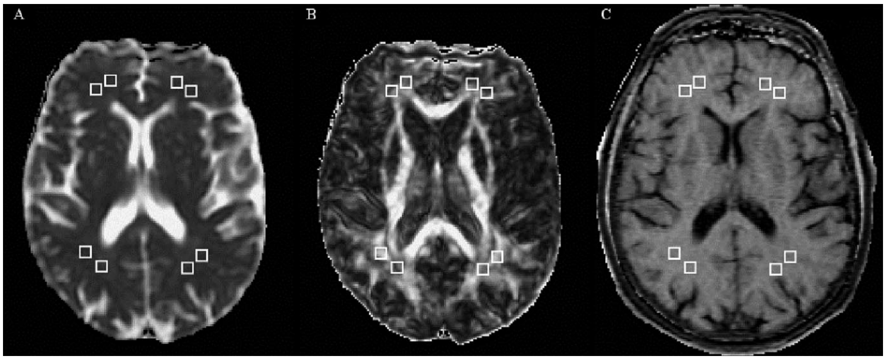

Figure 2. Examples of mean diffusivity, fractional anisotropy, and magnetization transfer ratio parametric maps, with frontal and parieto-occipital white matter regions of interest overlaid, obtained at the same slice location as shown in the left-hand column in figure 1.

for <D>, FA, and MTR ($p < 0.001$). Bonferroni-adjusted pairwise comparisons (Student t test) showed that <D> was highest and FA lowest in frontal white matter, whereas MTR was highest in frontal and lowest in parieto-occipital regions.

Water diffusion tensor parameters and cognition. Table 2 shows the means (SD) of the cognitive and information processing tests' scores and their correlations with water diffusion tensor parameters. Generally, for frontal white matter, the cognitive test scores are not significantly associated with <D> and FA, the exceptions being Letter–Number Sequencing and Verbal Fluency with <D> and MMSE and choice reaction time SD with FA. There are no significant correlations between <D> and FA and cognitive test scores in the parieto-occipital region. There is a consistent pattern of larger correlations (with absolute values often around 0.4) with FA in the centrum semiovale. Occasional significant associations in other areas are more likely to be due to chance. In centrum semiovale, FA correlates significantly with IQ at age 11 and the National Adult Reading Test estimate of prior ability, with the MMSE (despite its near-to-perfect-score mean and the small variance in this nondemented sample), with four of the five tests of current cognitive function and the general cognitive ability factor derived from these, and three of the five measures of information processing. There were also significant correlations between centrum semiovale <D> and Letter–Number Sequencing, Verbal Fluency, and general cognitive ability. The zero-order correlation between centrum semiovale FA and general cognitive ability was 0.487; when the simple reaction time SD was partialed out, the correlation was 0.301. This represents an attenuation of 62% in the explained variance, and provides evidence that the efficiency of simple information processing might act as an intermediate phenotype between high-level cognitive test scores and the integrity of white matter as measured by DT-MRI. This is now explored further in a path analysis.

Figure 3 shows the results of the path analysis. Two issues are dealt with here, namely, whether the model fits well and what it means if it does. The model has a good fit to the data. The average of the off-diagonal absolute standardized residuals is 0.037, indicating that most of the covariance among the four variables is accounted for in the four paths shown in the model. The χ^2 for the model was 1.61 ($p = 0.45$); nonsignificant χ^2 values indicate good fit. The following fit indexes were obtained, with values greater than 0.9 indicating good fit: Bentler–Bonett normed fit index = 0.96; Bentler–Bonett nonnormed fit index = 1.03; and comparative fit index = 1.00. The model may be understood as follows. First, general cognitive ability at age 83 is related to the person's mental test score at age 11. Second, there is an association between centrum semiovale FA and simple reaction time SD and between simple reaction time SD and general cognitive ability at age 83. Therefore, the two contributions to cognitive ability at age 83 are original cognitive ability and white matter integrity, via the endophenotype of processing efficiency (tested using reaction time). Last, cognitive ability at age 11 and centrum semiovale FA at age 83 are not independent. As discussed below, the importance of the path analysis model is that it suggests that the bivariate association between centrum semiovale FA and general cognitive ability at age 83 can be fully accounted for by other variables.

MTR and cognition. Correlations between the cognitive and information processing tests' scores and MTR were generally not significant (data not shown). The only correlation was between parieto-occipital MTR and Letter–Number Sequencing ($r = 0.32$; $p = 0.04$). This finding is likely to be due to chance.

Discussion. Large-scale, distributed, cortical processing networks have been suggested as a basis for cognition.[33] In this model of brain function, white matter fibers play the crucial role of linking the various components of the distributed processing system together. Any disruption of the white matter tracts might be expected to lead to a loss of functional "connectivity" between cortical regions and hence potentially to reduced cognitive function.[11] DT-MRI and MT-MRI are imaging modalities uniquely placed to investigate how normal aging affects white matter connectivity as they provide different, but complementary, measures of white matter integrity. In those studies that have measured how <D>, FA, and MTR change in normal aging,[29,34-37] the general finding is that <D> increases and FA and MTR decrease, indicating an age-related microstructural deterioration of white matter fiber coherence. By studying a group of subjects with a very narrow age range, as done here, these gross age-related changes are minimized, thereby allowing more subtle associations between these imaging correlates of white matter integrity and individual differences in cognitive ability to be investigated.

The DT-MRI results presented above provide support for the stated hypotheses that white matter in-

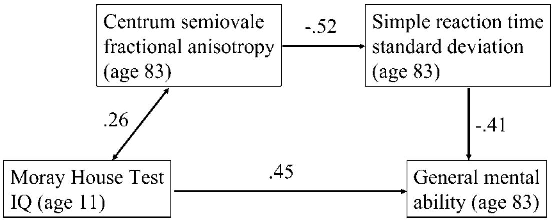

Figure 3. Path diagram showing possible influences among childhood and old age cognitive ability, efficiency of information processing (simple reaction time SD), and integrity of white matter assessed by fractional anisotropy in the centrum semiovale.

tegrity is related to 1) cognitive ability in youth, 2) cognitive ability in old age, and 3) efficiency of information processing. First, these data replicate the previous highly provocative finding that centrum semiovale FA correlates with IQ at age 11 and with an estimate of prior ability.[12] (The current report has only one subject in common with this previous study, and that subject provided new data here.) This implies that considering adult cognitive ability without knowing childhood cognition may partly obscure the etiology of MRI changes associated with aging. Second, significant correlations were found between centrum semiovale FA and four of the five individual tests for old age cognitive ability, general cognitive ability, and the MMSE. The consistency of these data provides further evidence for a relationship between water diffusion tensor parameters and cognitive ability in old age. The significant correlations between frontal white matter <D> and centrum semiovale <D> and FA with Verbal Fluency and Letter–Number Sequencing also confirm the possible association between water diffusion tensor parameters and executive function.[11,13] Third, centrum semiovale FA correlated significantly with three of the five measures of information processing (reaction time parameters and inspection time). After adjusting the correlation between centrum semiovale FA and general cognitive ability, the association was attenuated by 62%, providing evidence that the efficiency of simple information processing might act as an intermediate phenotype (endophenotype).

Little evidence was found, however, for correlations between white matter integrity, as measured by MT-MRI, and cognitive ability in youth and old age.[18] This might provide insight into how aging affects white matter microstructure. Extensive in vivo and in vitro experiments on various nonmyelinated neuronal fibers,[38,39] axons with large axoplasmic spaces,[40] and neurons in which fast axonal transport has been inhibited[38] indicate that the primary determinant of white matter anisotropic diffusion is the dense packing of axonal membranes with myelin playing a secondary role. As MTR does not exhibit the same significant correlations with tests of cognitive ability as centrum semiovale FA, it may be that changes in the degree of myelination or inflammatory effects, which have been shown in animal models to produce moderate reductions in MTR independent of alterations in myelin integrity,[41] are not as important as alterations to the spatial organization and coherence of the white matter fibers in cognitive aging. This view is challenged, however, by results from studies of cognitive decline in early relapsing–remitting multiple sclerosis (MS), which show that mean MTR of normal-appearing white matter is significantly associated with impairment of attention and information processing speed.[42] Alternatively, MTR may just not be as sensitive as <D> and especially FA in detecting subtle changes in cellular microstructure in normal aging. For example, table 1 shows that whereas <D> and FA vary significantly from region to region, MTR is almost constant. Nevertheless, further studies in larger cohorts are required before it can definitively be concluded that MT-MRI is not a useful tool for assessing cognitive ability.

A rare aspect of the current sample is the existence of cognitive test scores from both childhood and old age, and this afforded an investigation into how youthful cognitive ability influences cognitive aging. Specifically, in the path analysis presented in figure 3, when both age 11 IQ (prior mental ability) and simple reaction time SD (information processing efficiency) were accounted for in the correlation between general cognitive ability and centrum semiovale FA, the direct association was no longer significant. This model provides a potentially important theoretical advance in studies of cognitive aging. First, by finding that childhood IQ and centrum semiovale FA are related and that this accounts for a proportion of the association between centrum semiovale FA and cognition in old age, it suggests that the life-long stable trait of cognitive ability is associated with white matter integrity. This warrants further research on water diffusion tensor parameters and cognition in healthy younger subjects, in whom it is already known that aspects of brain structure and function relate to intelligence differences. Second, by finding that a measure of information processing efficiency (simple reaction time SD) mediates the association between centrum semiovale FA and cognition in old age, there is some evidence for one biologic foundation of the much-replicated finding that indices of

Table 1 *Mean (SD) values of mean diffusivity (<D>), fractional anisotropy (FA), and magnetization transfer ratio (MTR) for normal-appearing frontal and parieto-occipital periventricular white matter and centrum semiovale*

	Frontal white matter	Parieto-occipital white matter	Centrum semiovale
<D>, $\times 10^{-6}$ mm^2/s	857 (39)	801 (36)	761 (31)
FA	0.32 (0.03)	0.41 (0.04)	0.43 (0.05)
MTR,* %	33.9 (0.9)	33.0 (0.7)	33.2 (0.8)

* The degree of direct saturation of the water spins resulting from the MT pulse was measured at 0.2% from the CSF of five subjects chosen at random.

Table 2 *Mean (SD) values of cognitive and information processing tests and their correlations (Pearson r and p value) with water diffusion tensor parameters for normal-appearing frontal and parieto-occipital periventricular white matter and centrum semiovale*

	Frontal white matter		Parieto-occipital white matter		Centrum semiovale		Mean (SD) test scores
	<D>	FA	<D>	FA	<D>	FA	
Prior ability and dementia screen tests							
Age 11 IQ (Moray House Test)	−0.13	0.24	0.08	0.17	−0.21	0.37*	101.6 (15.6)
National Adult Reading Test	−0.19	0.08	−0.08	0.03	−0.14	0.42†	36.6 (8.7)
Mini-Mental State Examination	−0.22	0.32*	0.07	0.24	−0.13	0.41†	28.4 (1.7)
Assessments of current ability							
Raven Matrices	−0.18	0.28	0.15	0.23	−0.27	0.38*	31.9 (10.9)
Letter–Number Sequencing	−0.35*	0.09	−0.04	0.28	−0.35*	0.41†	10.4 (3.3)
Logical Memory	−0.03	−0.09	0.06	−0.12	0.04	0.15	37.4 (13.6)
Verbal Fluency	−0.46†	0.17	−0.18	0.16	−0.36*	0.56†	44.6 (15.9)
Digit Symbol	−0.14	0.14	0.19	0.10	−0.24	0.36*	44.0 (14.8)
General cognitive ability	−0.30	0.17	0.06	0.19	−0.32*	0.49†	0.00 (1.00)
Information processing tests							
Simple reaction time mean	0.23	−0.14	−0.08	0.16	0.17	−0.45†	297.2 (56.0)
Simple reaction time SD	0.17	−0.12	−0.05	−0.07	0.16	−0.52†	75.7 (58.4)
Choice reaction time mean	0.28	−0.26	−0.00	−0.18	0.28	−0.40†	748.2 (140.7)
Choice reaction time SD	0.13	−0.33*	0.00	−0.12	0.16	−0.21	159.5 (52.7)
Inspection time	−0.09	0.18	0.10	0.26	−0.26	0.27	103.9 (12.4)

* Correlations significant at the $p < 0.05$ level.
† Correlations significant at the $p < 0.01$ level.

<D> = mean diffusivity; FA = fractional anisotropy.

processing speed account for much of the variation in cognitive aging.[5,6] Also, reaction time indexes provide a simpler, intermediate phenotype to help our understanding of the association between water diffusion tensor parameters and higher-level cognitive test scores.[14] In summary, it would appear that centrum semiovale FA relates to cognition in old age because 1) people with higher psychometric intelligence have perennially higher FA values and 2) higher centrum semiovale FA in old age affords more efficient processing of information. However, these conclusions must be considered tentative because of the modest number of subjects in the current study.

This raises a further question as to why most of the significant correlations between cognitive tests scores and water diffusion tensor parameters are seen in centrum semiovale, and not the other two brain regions. (Indeed, the inconsistency of correlations in areas other than the centrum semiovale indicates that the occasional significant findings might be due to chance.) As with all studies of regional brain differences, the results will be influenced by regional sensitivity to the underlying biology and analysis methods. For example, in regions where the fiber orientation is homogeneous and FA is high, it is likely that there is increased statistical power to detect significant differences between individuals and populations. Conversely, in regions where multiple fibers cross and FA is reduced, the complex underlying white matter architecture provides an additional confound. Of the three regions studied, centrum semiovale has perhaps the most homogeneous fiber orientation, with fibers aligned predominantly in the superior/inferior direction.[43] The presence of white matter lesions, which, although not extensive, are most prevalent in frontal regions in these elderly subjects, further complicates the situation, as <D> is increased and FA decreased in these regions.[13] Although we avoided placing ROIs on obviously abnormal white matter, it is inevitable that some white matter lesions will have been included in the ROIs, especially in frontal regions. These factors, in addition to the observation that prefrontal white matter is more vulnerable to age-related degeneration than temporal/parietal fibers,[37] are reflected in table 1, where centrum semiovale has the highest FA and lowest <D> of the three regions studied. For these reasons, it is the region most likely to provide robust relationships between water diffusion tensor parameters and test scores in both youth and old age.

ROI methodology may also introduce more variance into the measurement of FA. This is because FA varies significantly across fiber bundles owing to partial volume and other effects, so even subtle variations in ROI placement may produce marked differences in the measured FA values.[44] Defining the ROI co-ordinates in Talairach space and determining the corresponding location in the subject's native space could address this problem,[37] if registration of elderly brains to a standard template can be performed accurately. However, once again, the presence of white matter lesions makes this approach far more problematic than in younger people.

Finally, as brain atrophy is a feature not only of normal aging but also of neurodegenerative diseases such as MS and Alzheimer disease (AD), these data may also have some relevance to studies investigating relationships between early cognitive decline and white matter loss in these pathologies. There are several studies in the literature reporting correlations between white matter water diffusion tensor parameters and cognitive decline in MS and AD. For example, in 34 patients with mildly disabling relapsing–remitting MS, significant correlations were found between normal-appearing white matter <D> and Verbal Fluency and Symbol Digit Modalities Test,[45] whereas <D>, FA, and the three eigenvalues of D measured in the posterior cingulate gyrus correlated with MMSE score in 34 patients with AD.[46] However, measurements of water diffusion tensor parameters in both gray and white matter structures in groups of normal older subjects (60 years and above) and age-matched patients with AD and mild cognitive impairment indicate that the pattern of changes in <D> and FA is different in normal aging and dementia.[47,48] This suggests that the mechanisms underlying age-associated cognitive decline may be different from those responsible for AD and mild cognitive impairment and that normal aging and dementia may not be part of a continuum of cognitive decline and degenerative structural change. A significant correlation between posterior fossa T2-weighted lesion volume and cognitive processing speed has been reported in patients with MS.[49] EPI-based susceptibility artifacts and lack of brain coverage in some subjects precluded an analysis of whether significant correlations exist between posterior fossa DT-MRI and MT-MRI parameters and cognitive ability in normal aging in the current study.

Acknowledgment

The authors thank Prof. J. Best for making clinical reports on the structural MRI scans. All MRI data were collected at the SHEFC Brain Imaging Research Centre for Scotland (http://www.dcn.ed.ac.uk/bic).

References

1. National Research Council. The aging mind: opportunities in cognitive research. Washington, DC: National Academy Press, 2000.
2. Hedden T, Gabrielli JD. Insights into the ageing mind: a view from cognitive neuroscience. Nat Rev Neurosci 2004;5:87–96.
3. Wilson RS, Beckett LA, Barnes LL. et al. Individual differences in rates of change in cognitive abilities of older persons. Psychol Aging 2002;17:179–193.
4. Salthouse TA, Ferrer-Caja E. What needs to be explained to account for age-related effects on multiple cognitive variables? Psychol Aging 2003;18:91–110.
5. Salthouse TA. The processing-speed theory of adult age differences in cognition. Psychol Rev 1996;103:403–428.
6. Salthouse TA. Aging and measures of processing speed. Biol Psychol 2000;54:35–54.
7. Tisserand DJ, Jolles J. On the involvement of prefrontal networks in cognitive ageing. Cortex 2003;39:1107–1128.
8. Bartzokis G. Age-related myelin breakdown: a developmental model of cognitive decline and Alzheimer's disease. Neurobiol Aging 2004;25:49–62.
9. Basser PJ. Inferring microstructural features and the physiological state of tissues from diffusion-weighted images. NMR Biomed 1995;8:333–344.
10. Moseley M. Diffusion tensor imaging and aging: a review. NMR Biomed 2002;15:553–560.
11. O'Sullivan, M, Jones DK, Summers PE, Morris RG, Williams SC, Markus HS. Evidence for cortical "disconnection" as a mechanism of age-related cognitive decline. Neurology 2001;57:632–638.
12. Shenkin SD, Bastin ME, MacGillivray TJ, Deary IJ, Starr JM, Wardlaw JM. Childhood and current cognitive function in healthy 80-year-olds: a DT-MRI study. Neuroreport 2003;14:345–349.
13. O'Sullivan, M, Morris RG, Huckstep B, Jones DK, Williams SCR, Markus HS. Diffusion tensor MRI correlates with executive dysfunction in patients with ischaemic leukoaraiosis. J Neurol Neurosurg Psychiatry 2003;75:441–447.
14. Deary IJ. Looking down on human intelligence: from psychometrics to the brain. Oxford: Oxford University Press, 2000.
15. Rovaris M, Filippi M, Minicucci L. et al. Cortical/subcortical disease burden and cognitive impairment in patients with multiple sclerosis. AJNR Am J Neuroradiol 2000;21:402–408.
16. van der Flier WM, van den Heuvel, DM, Weverling-Rijnsburger et al. Magnetization transfer imaging in normal aging, mild cognitive impairment, and Alzheimer's disease. Ann Neurol 2002;52:62–67.
17. Foong J, Symms MR, Barker GJ. et al. Neuropathological abnormalities in schizophrenia: evidence from magnetization transfer imaging. Brain 2001;124:882–892.
18. Armstrong CL, Traipe E, Hunter JV. et al. Age-related, regional, hemispheric, and medial-lateral differences in myelin integrity in vivo in the normal adult brain. AJNR Am J Neuroradiol 2004;25:977–984.
19. Scottish Council for Research in Education. The intelligence of Scottish children: a national survey of an age-group. London: University of London Press, 1933.
20. Deary IJ, Whiteman MC, Starr JM, Whalley LJ, Fox HC. The impact of childhood intelligence on later life: following up the Scottish Mental Surveys of 1932 and 1947. J Pers Soc Psychol 2004;86:130–147.
21. Nelson HE, Willison JR. National Adult Reading Test (NART) test manual (part II). Windsor, UK: NFER-Nelson, 1991.
22. Folstein MF, Folstein SE, McHugh PR. Mini-Mental State: a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.
23. Wechsler D. Wechsler Adult Intelligence Scale–III^{UK}. London, UK: Psychological Corp., 1998.
24. Lezak, M. Neuropsychological resting. 3rd ed. Oxford: Oxford University Press, 1995.
25. Raven JC, Court JH, Raven J. Manual for Raven's Progressive Matrices and Vocabulary Scales. London, UK: H. K. Lewis, 1977.
26. Wechsler D. Wechsler Memory Scale–III^{UK}. London, UK: Psychological Corp., 1998.
27. Deary IJ, Der G, Ford G. Reaction times and intelligence differences: a population-based cohort study. Intelligence 2001;29:389–399.
28. Deary IJ, Simonotto E, Meyer M. et al. The functional anatomy of inspection time: an event-related fMRI study. Neuroimage 2004;22:1466–1479.
29. Silver NC, Barker GJ, MacManus DG, Tofts PS, Miller DH. Magnetisation transfer ratio of normal brain white matter: a normative database spanning four decades of life. J Neurol Neurosurg Psychiatry 1997;62:223–228.
30. Basser PJ, Pierpaoli C. A simplified method to measure the diffusion tensor from seven MR images. Magn Res Med 1998;39:928–934.
31. Jenkinson M, Smith S. A global optimisation method for robust affine registration of brain images. Med Image Anal 2001;5:143–156.
32. Basser PJ, Mattiello J, LeBihan D. Estimation of the effective self-diffusion tensor from the NMR spin echo. J Magn Res B 1994;103:247–254.
33. Mesulam MM. Large-scale neurocognitive networks and distributed processing for attention, language, and memory. Ann Neurol 1990;28:597–613.
34. Nusbaum AO, Tang CY, Buchsbaum MS, Wei TC, Atlas SW. Regional and global changes in cerebral diffusion with normal aging. AJNR Am J Neuroradiol 2001;22:136–142.
35. Abe O, Aoki S, Hayashi N. et al. Normal aging in the central nervous system: quantitative MR diffusion-tensor analysis. Neurobiol Aging 2002;23:433–441.
36. Rovaris M, Iannucci G, Cercignani M. et al. Age-related changes in conventional, magnetization transfer, and diffusion-tensor MR imaging findings: study with whole-brain tissue histogram analysis. Radiology 2003;227:731–738.
37. Salat DH, Tuch DS, Greve DN. et al. Age-related alterations in white matter microstructure measured by diffusion tensor imaging. Neurobiol Aging 2005;26:1215–1227.
38. Beaulieu C, Allen PS. Determinants of anisotropic water diffusion in nerves. Magn Res Med 1994;31:394–400.

39. Huppi PS, Maier SE, Peled S. et al. Microstructural development of human newborn cerebral white matter assessed in vivo by diffusion tensor magnetic resonance imaging. Pediatr Res 1998;44:584–590.
40. Beaulieu C, Allen PS. Water diffusion in the giant axon of the squid: implications for diffusion-weighted MRI of the nervous system. Magn Res Med 1994;32:579–583.
41. Brochet B, Dousset V. Pathological correlates of magnetization transfer imaging abnormalities in animal models and humans with multiple sclerosis. Neurology 1999;53:S12–S17.
42. Deloire MS, Salort E, Bonnet M. et al. Cognitive impairment as marker of diffuse brain abnormalities in early relapsing remitting multiple sclerosis. J Neurol Neurosurg Psychiatry 2005;76:519–526.
43. Wakana S, Jiang H, Nagae-Poetscher LM, van Zijl, PC, Mori S. Fiber tract-based atlas of human white matter anatomy. Radiology 2004;230: 77–87.
44. Pfefferbaum A, Sullivan EV. Increased brain white matter diffusivity in normal adult aging: relationship to anisotropy and partial voluming. Magn Res Med 2003;49:953–961.
45. Rovaris M, Iannucci G, Falautano M. et al. Cognitive dysfunction in patients with mildly disabling relapsing-remitting multiple sclerosis: an exploratory study with diffusion tensor MR imaging. J Neurol Sci 2002;195:103–109.
46. Yoshiura T, Mihara F, Ogomori K, Tanaka A, Kaneko K, Masuda K. Diffusion tensor in posterior cingulate gyrus: correlation with cognitive decline in Alzheimer's disease. Neuroreport 2002;13:2299–2302.
47. Fellgiebel A, Wille P, Muller MJ. et al. Ultrastructural hippocampal and white matter alterations in mild cognitive impairment: a diffusion tensor imaging study. Dement Geriatr Cogn Disord 2004;18:101–108.
48. Head D, Buckner R, Shimony JS. et al. Differential vulnerability of anterior white matter in nondemented aging with minimal acceleration in dementia of the Alzheimer type: evidence form diffusion tensor imaging. Cerebral Cortex 2004;14:410–423.
49. Archibald CJ, Wei X, Scott JN. et al. Posterior fossa lesion volume and slowed information processing in multiple sclerosis. Brain 2004;127: 1526–1534.