White Matter Microstructural Integrity and Cognitive Function in a General Elderly Population

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Context: The role of macrostructural white matter changes, such as atrophy and white matter lesions, in cognitive decline is increasingly being recognized. However, in the elderly population, these macrostructural changes do not account for all variability in cognition. Measures reflecting white matter microstructural integrity may provide additional information to investigate the relation between white matter changes and cognition.

Objective: To study the relation between white matter integrity and cognition in the general elderly population, using diffusion tensor imaging and taking into account macrostructural white matter changes.

Design: Cross-sectional population-based study.

Setting: A general community in the Netherlands.

Participants: A population-based sample of 860 persons, older than 60 years, free of dementia. We performed multisequence magnetic resonance imaging, which included diffusion tensor imaging, and extensive neuropsychological testing. Fractional anisotropy, mean diffusivity, and directional diffusivities were measured globally in white matter lesions and normal-appearing white matter.

Main Outcome Measures: Performance on neuropsychological tests in the following cognitive domains: memory, executive function, information processing speed, global cognition, and motor speed.

Results: Regardless of macrostructural white matter changes, a higher mean diffusivity or higher axial and radial diffusivities within white matter lesions or normal-appearing white matter were related to worse performance on tasks assessing information processing speed and global cognition. In addition, diffusivity within white matter lesions related to memory, while in normal-appearing white matter, it furthermore related to executive function. Lower mean fractional anisotropy in white matter lesions or normal-appearing white matter related to worse information processing speed and motor speed.

Conclusions: Microstructural integrity of both white matter lesions and normal-appearing white matter is associated with cognitive function, regardless of white matter atrophy and white matter lesion volume. This suggests that measuring white matter integrity has added value beyond macrostructural assessment of white matter changes to study the relation between white matter and cognition.

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tional pathologic studies have found that the degree of axonal and myelin damage within white matter lesions with similar appearance on conventional MRI is highly variable. It may thus be that in their effect on cognition some white matter lesions are worse than others, which cannot be deferred from the mere number or volume of lesions. Measures reflecting microstructural integrity of white matter may provide additional information, beyond macrostructural changes, on the relation between white matter and cognition. Diffusion tensor imaging (DTI) is an MRI technique that enables the measurement of diffusion of water molecules within the brain. In normal white matter, the motion of water molecules is restricted by the parallel-oriented fibers and diffusion is therefore highly anisotropic. Degradation of the microstructural organization in white matter is accompanied by changes in measurable DTI parameters, more specifically by a decrease in fractional anisotropy (FA) and an increase in mean diffusivity (MD). There is pathologic evidence that FA and MD correlate directly with the amount of myelin in the white matter and to a lesser extent also to axonal count. Animal studies have suggested a primary role of axonal membranes rather than presence of myelin in anisotropy. Diffusion tensor imaging therefore provides a noninvasive assessment of white matter microstructural integrity and as such may be used to quantify the severity of tract disruption caused by white matter lesions and white matter atrophy. Furthermore, results from animal studies have indicated that analysis of directional diffusivities—axial ($\lambda_a$) and radial ($\lambda_r$)—may provide additional information on the potential underlying pathophysiology of the white matter changes. In these studies, myelin breakdown related to increased diffusivity perpendicular to the white matter tract ($\lambda_r$), while axonal damage was reflected in diffusivity changes parallel ($\lambda_a$) to the primary fiber orientation.

Also, DTI may be able to measure changes in the normal-appearing white matter (NAWM) before these can be visualized using conventional MRI. Small studies in healthy individuals, generally comparing the very young with elderly persons, have shown significant decreases of FA and increases of MD with age. Several other studies, likewise limited in size, have found correlations between DTI parameters (for the greater part measured in regions of interest [ROIs]) and cognitive function. None of these studies accounted for volumetric microstructural white matter changes when studying DTI in relation to cognitive function in a general elderly population. There have been 2 larger population-based studies in elderly individuals, both comprising a little more than 100 individuals, investigating the relation of DTI with cognition. Though one of these studies adjusted for visually graded white matter lesion load, neither study took atrophy of the NAWM or volume of white matter lesions into account. In the current study, we therefore investigated in a large sample of the population-based Rotterdam Scan Study the association of FA and MD in white matter lesions and in global NAWM with performance on tests of cognitive function, and we assessed whether this association was independent of white matter atrophy and of white matter lesion burden.

### METHODS

#### PARTICIPANTS

The study is based on participants from the Rotterdam Study, a population-based cohort study in the Netherlands that is aimed at investigating determinants of various chronic diseases among elderly persons. The original study population (n=7983) consisted of the general population 55 years and older within the Ommoord area, a suburb of Rotterdam. In 2000, the cohort was expanded with 3011 persons (≥55 years) who were living in the study area and had not been included before. From August 2005 to May 2006, we randomly selected 1073 members of this cohort expansion for participation in the Rotterdam Scan Study, a prospective brain MRI study that is embedded within the Rotterdam Study. The institutional review board (Eramus MC, Rotterdam, the Netherlands) approved the study. We excluded individuals with dementia (n=4) or those who had MRI contraindications (n=94). A total of 975 persons were eligible, of whom 907 participated and gave written informed consent. Because of physical disabilities, imaging could not be performed in 12 individuals. A total of 895 complete MRI examinations were performed.

#### MRI PROTOCOL

We performed a multisquence MRI protocol on a 1.5-T MRI scanner (General Electric Healthcare, Milwaukee, Wisconsin). All participants were scanned on the same scanner, and during the entire study period, no software or hardware upgrades were performed on the system. For DTI, we used a single-shot, diffusion-weighted spin echo echo-planar imaging sequence (repetition time [TR]=8000 milliseconds, echo time [TE]=80.0 milliseconds, field of view [FOV]=21×21 cm², matrix=96×64 [interpolated to 128×128], slice thickness=3.3 mm, 36 contiguous slices, applying parallel imaging with acceleration factor=2, acquired voxel size=2.2×3.3×3.3 mm³, interpolated voxel size=1.6×1.6×3.5 mm³). Maximum b value was 1000 seconds/mm² in 25 noncollinear directions (number of excitations [NEX]=1), and 1 volume was acquired without diffusion weighting (b value=0 seconds/mm²). Acquisition time was 3:44 minutes. We further performed 3 high-resolution axial MRI sequences, ie, a T1-weighted 3-dimensional fast radiofrequency spoiled gradient recalled acquisition in steady state with an inversion recovery prepulse sequence (TR=13.8 milliseconds, TE=2.8 milliseconds, inversion time=400 milliseconds, FOV=25×17.5 cm², matrix=416×256 [interpolated to 512×512], flip angle=20°, NEX=1, bandwidth [BW]=12.50 kHz, 90 slices with a thickness=1.6 mm zero-padded in the frequency domain to 0.8 mm, interpolated voxel size=0.5×0.5×0.8×0.2 mm³), a proton density (PD)–weighted sequence (TR=12300 milliseconds, TE=17.3 milliseconds, FOV=25×17.5 cm², matrix=416×256, NEX=1, BW=17.86 kHz, 90 slices with slice thickness=1.6 mm), and a fluid-attenuated inversion recovery (FLAIR) sequence (TR=8000 milliseconds, TE=120 milliseconds, inversion time=2000 milliseconds, FOV=25×25 cm², matrix=320×224, NEX=1, BW=31.25 kHz, 64 slices with slice thickness=2.5 mm). All slices were contiguous.

#### TISSUE SEGMENTATION OF WHITE MATTER LESIONS AND NAWM

Structural MRI scans (T1-weighted, PD-weighted, FLAIR) were transferred onto a Linux workstation. Preprocessing steps and the classification algorithm have been described elsewhere. In summary, preprocessing included coregistration, nonuniformity cor-
Dimensions were calculated by summing all voxels (0.2 mm³ each) of normal-appearing white matter and cerebrospinal fluid. Volumes of NAWM and white matter lesions were defined as the sum of gray matter, NAWM, white matter lesions, and cerebrospinal fluid. White matter lesions were classified as a separate tissue class using the same method. All segmentation results were visually inspected (this required on average 1 minute per scan) and, if needed, manually corrected (needed in 68 scans [7.9%]; correction took on average 20 minutes per scan). To remove noncerebral tissue, e.g., eyes, skull, and cerebellum, we applied nonrigid registration to register to each brain a template scan in which these tissues were manually masked (creation of this template scan took 2 hours). Intracranial volume was calculated by summing the total volume of each tissue class by the intracranial volume. Because NAWM volume was highly correlated with total white matter volume (ie, the sum of NAWM and white matter lesions) (Pearson r = 0.991), we used relative NAWM volume as a measure of white matter atrophy.

### TEMPORAL LOBE ATROPHY

We assessed temporal lobe atrophy using a previously described protocol, in which a template brain with labels for the various lobes was nonrigidly registered to all scans. Brain tissue volume for both left and right temporal lobes was summed and expressed as a percentage of intracranial volume, yielding relative temporal lobe volume (and reflecting temporal lobe atrophy).

### POSTPROCESSING OF DTI DATA

The DTI data were processed using the FMRIB toolbox FSL (http://www.fmrib.ox.ac.uk/fsl/). Eddy current and head-motion correction were performed in FSL by means of an affine registration to the reference (b0) volume. The corrected data were skull-stripped by applying the FSL Brain Extraction Tool on both the b0 and the diffusion-weighted images. Next, a tensor model was fitted to the diffusion data using the FMRIB Diffusion Toolbox to yield FA, MD, and both axial (λ1) and radial [(λ2 + λ3)/2] diffusivities. The DTI maps were resampled and coregistered to the structural images (at the resolution of T1-weighted images: 0.5 × 0.5 × 0.8 mm³) using mutual information. Use of the MD and T1-weighted image pair in the coregistration gave the best result, as this map is morphologically more similar to the structural images. The final registration result in each scan was checked visually for errors (this visual check took on average 1 minute per scan). The transformation parameter used in the MD-T1 transform was saved and applied to the coregistered FA and directional diffusivity images. The Figure shows a typical example of FA and MD maps registered to the structural images and a tissue segmentation result of the same person.

### TISSUE SEGMENTATION

Tissue segmentation results for white matter lesions and NAWM were then combined with the diffusion maps, and histograms of FA, MD, λ₁, and λ₂ were created for both tissue classes. Histograms were normalized by dividing the number of voxels in each bin by the total amount of voxels. To minimize noise from partial volume effects of cerebrospinal fluid or gray matter, we set a threshold for FA in NAWM to contain white matter only (voxels with FA value < 0.20 were excluded from all maps [FA, MD, and λ₁, and λ₂]) (Figure). Both for white matter lesions and NAWM, we derived the mean FA, MD, λ₁, and λ₂, and the full-width at half maximum for each DTI measure from the peaks in the intensity histogram.

Tissue segmentation or DTI postprocessing was not possible in 35 scans because of severe motion artifacts or susceptibility artifacts from metallic objects, leaving a total of 860 useable scans.

### ASSESSMENT OF COGNITIVE FUNCTION

Cognitive function was assessed with the following neuropsychological test battery: the Mini-Mental State Examination, a 15-word verbal learning test (based on the Rey recall of words), the Stroop test, the Letter-Digit Substitution Task (LDST), the Purdue Pegboard Test, and a word fluency test (animal categories). We generated sex-specific z scores (individual test score minus mean test score divided by the standard deviation) for each cognitive test. To obtain more robust measures, we constructed compound scores for memory, executive function, information processing speed, global cognition, and motor speed. The z scores for the Stroop tasks were inverted for use in these compound scores, as higher scores on...
the Stroop task indicate a worse performance while higher scores of the Stroop task (average of all 3 subtasks), the LDST, the word fluency test, and the immediate and delayed recall of the 15-word verbal learning test. Motor speed was defined by the Purdue Pegboard Test (both hands).

## LEVEL OF EDUCATION

During the initial interview at study entry, the attained level of education was assessed according to the standard classification of education. In our analysis, we combined the 4 highest levels into 1 category, thus, obtaining 4 levels: (1) primary education; (2) low-level vocational training; (3) medium-level secondary education; and (4) medium-level vocational training to university level.

## INFARCTS ON MRI

Presence of infarcts on MRI was assessed on structural MRI images. Lacunar infarcts were defined as focal lesions 3 mm or more and less than 15 mm in size with the same signal characteristics as cerebrospinal fluid on all sequences and, when located supratentorially, with a hyperintense rim on the FLAIR sequence. Lesions 15 mm or more in size, but otherwise similar, were rated as subcortical infarcts. Infarcts showing involvement of cortical gray matter were classified as cortical infarcts.

## CARDIOVASCULAR RISK FACTORS

Information on potentially confounding cardiovascular risk factors (systolic and diastolic blood pressure, smoking status, diabetes mellitus, serum total cholesterol level, and use of antihypertensive medication and lipid-lowering drugs) was collected as described previously.

## DATA ANALYSIS

Relative volume of white matter lesions was natural log transformed because of skewness of the untransformed measure. Within the random subset of 1073 persons invited to participate in this study, we compared demographic data and cognitive test results between those who participated (n=860) and those who did not participate (eg, not eligible for inclusion [n=98] or refusing to participate [n=68]) or persons in whom MRI could not be completed (n=12) or showed severe artifacts (n=35). For this comparison, we used unpaired t tests for continuous variables or χ² tests for dichotomous variables. We first checked whether there were any outliers by eyeballing the data and subsequently we checked for linearity in the relation of DTI parameters and cognition by performing analyses in quartiles of the distribution (data not shown). Because we assessed no deviation from linearity, we used multiple linear regression models to evaluate the association of DTI parameters in white matter lesions and in NAWM with performance in all cognitive domains. All analyses were adjusted for age, sex, and level of education. To investigate whether DTI parameters were associated with cognitive function regardless of macrostructural white matter changes, we additionally adjusted analyses for relative volumes of NAWM and white matter lesions. Also, we investigated the effect of additionally adjusting analyses for cardiovascular risk factors and we tested for interaction of sex on the relation between DTI parameters and cognition. We furthermore studied whether results changed when we additionally excluded persons with lacunar or cortical infaracts. Finally, we examined results when adjusting additionally for temporal lobe atrophy. Because results for full-width at half maximum did not differ from those for the means of the DTI parameters, we present only results for the means.

## RESULTS

The characteristics of the study population (n=860) are shown in Table 1. Mean age was 67.3 years (range, 60.7-91.7 years) and 50.6% were women. Nonparticipants were significantly older, had lower education, and, though not reaching significance, performed slightly worse on all cognitive tests than persons who participated.

In white matter lesions, mean [SD] FA values were lower (0.25 [0.03]) and MD values were higher (1.25 [0.11] × 10⁻³ mm²/s) compared with NAWM (mean [SD] FA 0.37 [0.01] and MD 0.76 [0.03] × 10⁻³ mm²/s). The correlation between volumes of NAWM or white matter lesions and DTI parameters is shown in Table 2. Tissue volumes and DTI parameters were all significantly correlated, but some correlations were stronger than others and the correlation of white matter lesion volume with MD and FA within lesions was inverse compared with...
the correlation of NAWM volume with DTI parameters of NAWM (Table 2). Within NAWM and white matter lesions, MD and FA were highly correlated, even more so in NAWM than in white matter lesions (Table 2).

Women had slightly lower values of MD in both NAWM and white matter lesions compared with men (in NAWM, mean age-adjusted difference in MD for women compared with men was \(-0.006\) [95% confidence interval, \(-0.010\) to \(-0.003\)] and in white matter lesions, the difference in MD was \(-0.016\) [95% confidence interval, \(-0.030\) to \(-0.003\)]. There was no sex difference for FA values in either NAWM or white matter lesions.

**Table 2. Pearson Correlation Coefficients for NAWM or WML Volumes and DTI Parameters**

<table>
<thead>
<tr>
<th></th>
<th>NAWM Volume</th>
<th>WML Volume</th>
<th>WML, Mean MD</th>
<th>WML, Mean FA</th>
<th>WML, Mean (\lambda_{ax})</th>
<th>WML, Mean (\lambda_{rad})</th>
<th>NAWM, Mean MD</th>
<th>NAWM, Mean FA</th>
<th>NAWM, Mean (\lambda_{ax})</th>
<th>NAWM, Mean (\lambda_{rad})</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAWM volume</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>WML volume</td>
<td>(-0.20)</td>
<td>(-0.27)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>WML, mean MD</td>
<td>(-0.16)</td>
<td>(-0.23)</td>
<td>(-0.60)</td>
<td>(-0.39)</td>
<td>(-0.71)</td>
<td>(0.92)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>WML, mean FA</td>
<td>(0.08)</td>
<td>(0.22)</td>
<td>(0.97)</td>
<td>(0.24)</td>
<td>(0.24)</td>
<td>(0.23)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>WML, mean (\lambda_{ax})</td>
<td>(-0.15)</td>
<td>(-0.28)</td>
<td>(-0.15)</td>
<td>(-0.11)</td>
<td>(0.31)</td>
<td>(0.27)</td>
<td>(0.97)</td>
<td>(-0.71)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>WML, mean (\lambda_{rad})</td>
<td>(-0.33)</td>
<td>(0.36)</td>
<td>(0.24)</td>
<td>(0.20)</td>
<td>(0.20)</td>
<td>(0.20)</td>
<td>(0.99)</td>
<td>(-0.81)</td>
<td>(0.91)</td>
<td>...</td>
</tr>
<tr>
<td>NAWM, mean MD</td>
<td>(0.09)</td>
<td>(-0.27)</td>
<td>(-0.01)</td>
<td>(0.22)</td>
<td>(0.04)</td>
<td>(-0.04)</td>
<td>(-0.71)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>NAWM, mean FA</td>
<td>(-0.38)</td>
<td>(0.33)</td>
<td>(0.29)</td>
<td>(0.20)</td>
<td>(-0.17)</td>
<td>(0.20)</td>
<td>(0.99)</td>
<td>(-0.81)</td>
<td>(0.91)</td>
<td>...</td>
</tr>
<tr>
<td>NAWM, mean (\lambda_{ax})</td>
<td>(-0.32)</td>
<td>(0.37)</td>
<td>(0.20)</td>
<td>(-0.17)</td>
<td>(0.20)</td>
<td>(0.20)</td>
<td>(0.99)</td>
<td>(-0.81)</td>
<td>(0.91)</td>
<td>...</td>
</tr>
</tbody>
</table>

Abbreviations: DTI, diffusion tensor imaging; FA, fractional anisotropy; ICV, intracranial volume; MD, mean diffusivity; NAWM, normal-appearing white matter; WML, white matter lesion; \(\lambda_{ax}\), axial diffusivity; \(\lambda_{rad}\), radial diffusivity.

*a* Expressed as percentage of intracranial volume.

*b* Natural log transformed.

*c* Correlation is significant at the .01 level.

*d* Correlation is significant at the .05 level.

Additional adjustment for cardiovascular risk factors had very little effect on the associations (Table 3 and Table 4). There was no interaction between sex and DTI parameters in their effect on cognition. Persons with lacunar or cortical infarcts had on average a higher median relative white matter lesion volume (0.61%) (Figure) than persons without infarcts (0.26%). Despite this, additional exclusion of persons with lacunar or cortical infarcts did not change any of the associations presented in Table 3 and Table 4. Also, additional adjustment for temporal lobe atrophy did not change any of the results (Table 3 and Table 4).

In our study, microstructural integrity of white matter lesions and NAWM as assessed by DTI was associated with performance on tests measuring cognitive function, regardless of white matter atrophy and white matter lesion volume.

Strengths of our study are the large sample size of elderly subjects and the population-based setting. We used a high-resolution MRI protocol and automated postprocessing techniques to segment volumes of NAWM and white matter lesions and to measure DTI parameters in white matter lesions and in NAWM. To minimize confounding by partial volume effect of gray matter and cerebrospinal fluid, we excluded voxels from NAWM with FA values too low (<0.20) to represent white matter. Mean values for FA and MD in white matter lesions and NAWM corresponded to previously published values that were obtained by operator-defined manual measurements.

There are some potential limitations that we should consider. First, our study is cross-sectional and thus interpretation of our results regarding cause and effect is limited. Because of time and scanner constraints, we acquired DTI images at lower resolution than structural images. Registration of DTI scans to tissue segmentation results may therefore have lost some precision. Because we measured global changes in NAWM and white matter lesions and ex-
included voxels with DTI values unlikely to represent white matter, we feel that this has not greatly influenced our results. Echoplanar imaging as performed in DTI suffers invariably from geometric distortions and susceptibility artifacts, which may also compromise accurate registration. We visually checked all registration results and did not observe problems related to distortion or susceptibility artifacts. This may be related to the use of parallel imaging in our automated pipeline, which precludes the drawing of conclusions on a regional level, this method is sufficient to suggest that changes in white matter lesion and NAWM microstructure occur and paves the way for a more detailed analysis of the relation between tissue DTI parameters and cognitive function. In future studies, it would be especially interesting to investigate whether changes in DTI parameters in white matter lesions and NAWM and did not further specify changes occurring at a regional level. It has been argued that a strength of histogram analysis such as we used is its ability to measure subtle diffuse disease, which we hypothesized to be present in NAWM. Also, the histogram analyses enabled us to automate the measurements in this large sample. Region-of-interest analysis, which is common practice in DTI analyses, suffers from subjective ROI placement and requires intensive manual labor. Though our results cannot be validated with ROI analysis (because of the whole-brain approach), we took care to ensure the quality of our automated measurements by incorporating visual inspection and manual correction steps. The time needed for this user interaction in our automated pipeline was on average only 3.5 minutes per scan. Despite the limitations of sampling large white matter areas as done in histogram analysis, which precludes the drawing of conclusions on a regional level, this method is sufficient to suggest that changes in white matter lesion and NAWM microstructure occur and paves the way for a more detailed analysis of the relation between tissue DTI parameters and cognitive function. In future studies, it would be especially interesting to investigate whether changes in DTI parameters in white matter lesions and NAWM and subsequent effect on cognitive function are more pronounced when occurring in certain brain locations.

There have been several previous studies reporting on the relation between DTI parameters in white matter and cognitive function in nondiseased individuals. With the exception of 2,22 these studies were invariably small and included only very young and very old individuals, thus generating large contrasts in age and cognitive function. Principally using ROI-based measurements, they assessed relations of FA or MD...
Table 4. Linear Regression Models for DTI Parameters in Normal-Appearing White Matter in Relation to Cognitive Function*  

<table>
<thead>
<tr>
<th>Model</th>
<th>Mean Change in FA in normal-appearing white matter</th>
<th>Mean Change in λax in normal-appearing white matter</th>
<th>Mean λrad in normal-appearing white matter</th>
<th>Mean MD in normal-appearing white matter</th>
<th>Mean MD in normal-appearing white matter</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ageb −0.02 (−0.04 to −0.01)c</td>
<td>Normal-appearing white matter volumeb,d</td>
<td>Model 1 −0.02 (−0.09 to 0.05)</td>
<td>Model 2 −0.02 (−0.10 to 0.05)</td>
<td>Model 3 −0.01 (−0.08 to 0.07)</td>
</tr>
<tr>
<td></td>
<td>0.01 (−0.07 to 0.07)</td>
<td>0.14 (0.09 to 0.20)c</td>
<td>−0.01 (−0.07 to 0.07)</td>
<td>−0.01 (−0.10 to 0.04)</td>
<td>−0.01 (−0.07 to 0.09)</td>
</tr>
<tr>
<td></td>
<td>0.15 (0.09 to 0.21)c</td>
<td>0.01 (−0.08 to 0.07)</td>
<td>0.00 (−0.07 to 0.08)</td>
<td>0.02 (−0.06 to 0.10)</td>
<td>0.01 (−0.07 to 0.08)</td>
</tr>
<tr>
<td></td>
<td>0.10 (0.05 to 0.15)c</td>
<td>0.00 (−0.15 to 0.04)</td>
<td>0.00 (−0.15 to 0.04)</td>
<td>0.02 (−0.16 to 0.04)</td>
<td>0.00 (−0.17 to 0.04)</td>
</tr>
<tr>
<td></td>
<td>0.09 (0.02 to 0.16)c</td>
<td>0.10 (−0.17 to 0.07)c</td>
<td>0.10 (−0.17 to 0.04)c</td>
<td>0.10 (−0.17 to 0.04)c</td>
<td>0.10 (−0.17 to 0.04)c</td>
</tr>
</tbody>
</table>

Abbreviations: DTI, diffusion tensor imaging; FA, fractional anisotropy; MD, mean diffusivity; λax, axial diffusivity; λrad, radial diffusivity.

*Model 1: adjusted for age, sex, and level of education. Model 2: same as model 1, additionally adjusted for normal-appearing white matter volume. Model 3: same as model 1, additionally adjusted for white matter lesion volume. Model 4: same as model 1, additionally adjusted for both normal-appearing white matter volume and white matter lesion volume. Model 5: same as model 4, additionally adjusted for systolic blood pressure, diastolic blood pressure, serum total cholesterol level, diabetes mellitus, smoking status, use of blood pressure-lowering drugs, and use of lipid-lowering drugs. Model 6: same as model 4, additionally adjusted for relative temporal lobe volume.

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with executive function,18,20,46 interhemispheric transfer time,50 attentional tasks,18,51 speed of processing,18,49 and speed of perception.19 Studies in small groups of patients with ischemic disease have shown a similar association between DTI parameters in white matter and cognitive function.62,52,53 In the larger Charlton et al21 population-based sample of 106 elderly individuals aged 50 to 90 years, DTI correlated, after controlling for age, with working memory but not with executive function or information processing speed. In their study, white matter volume or white matter atrophy was not taken into account. The equally sized study by Shenkin et al22 also found only associations with interhemispheric transfers.19 In small groups of patients with ischemic disease,19 results are in accordance with several studies in humans that also found increases of both λax and λrad diffusivities with age or white matter changes.14,15,16 Our results are in accordance with reports on the relation between macrostructural white matter changes and cognitive function, which show that the amount of white matter atrophy as well as white matter lesion volume have an important role in executive function and information processing speed.15,50 We furthermore found that MD
and directional diffusivities, but not FA, in white matter lesions were strongly related to performance on memory tasks. Though the role of white matter in memory is less reported, this finding is in line with small studies in patients with multiple sclerosis or chronic brain injury, which also found MD to be primarily related to memory.\textsuperscript{39,60} Furthermore, in patients with CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) and Alzheimer disease, MD in white matter lesions was found to be more strongly correlated with Mini-Mental State Examination scores than was FA.\textsuperscript{53,61}

Our results did not change when adjusting for temporal lobe atrophy. This may indicate that DTI parameters are more strongly related to cognitive function than are brain atrophy measures. However, we did not have the more specific measures of medial temporal lobe atrophy or hippocampal atrophy, which are known strong predictors of Alzheimer disease and, as such, cross-sectionally and longitudinally related to cognitive performance.\textsuperscript{63}

Although it is still largely unknown what exact processes underlie the changes in FA and MD that we measure with DTI, several pathologic studies support the notion that these DTI parameters reflect white matter breakdown.\textsuperscript{12} The rather weak correlations we assessed between macrostructural white matter changes and DTI parameters seem to confirm that MD and FA do not merely reflect atrophy or lesion formation. Although MD and FA are highly correlated in white matter lesions and even more so in NAWM, this correlation is not perfect and to what extent both of these parameters are indicative of common pathophysiology or whether they measure different events remains uncertain. The disparity in associations between both parameters with cognitive function suggests that both measures potentially reflect different pathophysiology. Though not supported by fundamental research, increased MD is generally hypothesized to indicate an increase in interstitial or extracellular fluid, as is present in, for example, edema, while a decrease in FA is thought to reflect more irreversible structural damage, such as axonal loss. This notion was supported by a study in patients with cerebral edema caused by hepatic encephalopathy who exhibited no decrease in FA but a significant increase in MD, which proved reversible after treatment.\textsuperscript{63} Though in animal studies, analysis of $\lambda_\text{s}$ and $\lambda_\text{ad}$ diffusivities reportedly provides additional information regarding the nature of white matter pathology,\textsuperscript{14} directional diffusivities are still poorly studied in humans, and thus, their implication is not fully understood.

We found strong associations between FA and especially MD and directional diffusivities with cognitive function, even when taking into account volume of white matter lesions and white matter atrophy. This indicates that the deleterious effect of white matter changes on cognition not only depends on lesion burden or amount of atrophy, but also on characteristics that are not easily evaluated by conventional MRI. This has important implications. First, it implies that DTI may aid in investigating whether white matter lesions that have a similar appearance on conventional MRI actually differ in pathophysiology and subsequently in their effect on cognitive function. Second, our data suggest that DTI may eventually be helpful in predicting which persons may have cognitive decline and thus identify persons who would benefit most from therapeutic intervention.

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