Mild Cognitive Impairment:

Cerebrospinal Fluid Tau Biomarker Pathologic Levels and Longitudinal Changes in White Matter Integrity[1]

Inge K. Amlien, Cand Psychol
Anders M. Fjell, PhD
Kristine B. Walhovd, PhD
Per Selnes, PhD
Vidar Stenset, PhD
Ramune Grambaite, PhD
Atle Bjørnerud, PhD
Paulina Due-Tønnessen, MD
Anders Skinningsrud, MD
Leif Gjerstad, PhD
Ivar Reinvang, PhD
Tormod Fladby, PhD

Purpose: To evaluate the relationship between *(a)* pathologic levels of cerebrospinal fluid (CSF) total tau as an index of the intensity of ongoing neuronal degeneration and *(b)* longitudinal changes in white matter (WM) integrity in patients with mild cognitive impairment (MCI).

Materials and Methods: Participants gave written informed consent, and the Norwegian committee for medical research ethics approved the study. Thirty patients with MCI and nonpathologic CSF total tau levels, nine patients with MCI and pathologic CSF total tau levels, and 16 age-matched healthy control subjects underwent diffusion-tensor imaging at baseline and after a mean follow-up of 2.6 years ± 0.54 (standard deviation), with range of 1.58–3.98 years. The effect of diagnosis (MCI vs no MCI) at baseline and CSF tau levels at fractional anisotropy (FA), mean diffusivity, radial diffusivity (D_R), and axial diffusivity were tested with tract-based spatial statistics. Differences in WM integrity at baseline and follow-up and change over time were compared among patients with pathologic CSF total tau levels (MCI high tau), patients with normal CSF total tau levels (MCI low tau), and healthy control subjects. Linear mixed-model between-group within-subject analyses were conducted to examine differences in rate of change over time in FA and D_R.

Results: Longitudinal analysis of regional WM change revealed significant decrease in FA ($P = .038$) and increase in D_R ($P = .018$) in the MCI high-tau group relative to control subjects. For D_R, the changes were regionally specific to the right cingulum and the right superior and inferior longitudinal fasciculi.

Conclusion: Reduction in WM integrity was greater in patients with MCI who had the most intense neuronal degeneration as indexed by using CSF total tau, suggesting that these patients might represent a subgroup of MCI with more intense WM degeneration who are possibly at greater risk of developing Alzheimer disease.

© RSNA, 2012

Increased cerebrospinal fluid (CSF) levels of the microtubule-associated protein tau are commonly found in mild cognitive impairment (MCI) and Alzheimer disease (AD) (1). Tau is primarily located in the axons. By binding to tubulin, tau plays an important role in stabilizing and promoting assembly of microtubules, which are involved in maintaining cell structure and serve as tracks for axonal transport (2). Heightened levels of CSF total tau are probably markers for ongoing axonal damage (3), and increased levels of CSF total tau are found in a range of neurodegenerative disorders in addition to AD, such as some cases of frontotemporal dementia and Creutzfeldt–Jakob disease (4), as well as after acute stroke (5).

The pathologic processes behind the increased levels of CSF total tau in AD also seem to affect white matter (WM) integrity. WM damage in AD-type dementia has long been known from postmortem studies (6), but only recently has in vivo quantification of WM integrity been possible by use of diffusion-tensor imaging (7). Researchers in several studies (8–10) have shown reduced WM integrity in MCI and AD, establishing diffusion-tensor imaging as a promising tool for early detection of AD. However, the relationship between pathologic CSF total tau levels (on the basis of age-dependent criteria) and WM integrity at predementia stages has been scarcely explored. Knowledge about this relationship would increase our understanding of the complexity of the mechanisms involved in MCI and early AD. In a previous cross-sectional region-of-interest–based study of the same patient population as in the present article, lower fractional anisotropy (FA) and higher radial diffusivity (D_R) were found in the posterior cingulum in patients with MCI with pathologic levels of CSF total tau compared with patients with normal levels and healthy control subjects (11). To our knowledge, in no other study have the researchers explicitly addressed the relationship between measures at diffusion-tensor imaging and established CSF biomarkers. Longitudinal data are required to determine whether pathologic CSF tau levels help in the prediction of further WM degeneration or instead are related to the burden of accumulated WM injury during years. Because increases in CSF tau are seen in acute conditions with neuronal and axonal damage (3,5), we hypothesized that patients with MCI who have the highest levels of CSF total tau (MCI high tau) would show greater reduction in WM integrity over time compared with patients who have normal levels (MCI low tau) and healthy control subjects. The purpose of the present study was to evaluate the relationship between (a) pathologic CSF total tau levels as an index of the intensity of ongoing neuronal degeneration and (b) longitudinal changes of WM integrity in patients with MCI.

Materials and Methods

Sample

This prospective study was approved by the Regional Committee for Medical and Health Research Ethics, Oslo, Southeast, Norway, and written informed consent was obtained (11–14). Thirty-nine patients with MCI (19 women, 20 men; mean age, 59.79 years ± 7.6 [standard deviation]) attending a university-based memory clinic and 16 control subjects (10 women, six men; mean age, 61.69 years ± 7.9) without deficits related to memory, emotionality, or cognitive tempo (primarily the patients' spouses) were included in the study. Participants were recruited consecutively between 2005 and 2009, with planned reassessment 2–3 years later. The last examination was performed in February 2011.

Inclusion criteria for the patients were age of 40–79 years and subjective

Advances in Knowledge

■ Longitudinal analysis of white matter (WM) integrity revealed significant declines in fractional anisotropy (P = .038) and increased radial diffusivity (P = .018) in patients with mild cognitive impairment (MCI) who had pathologic cerebrospinal fluid (CSF) total tau levels relative to control subjects for a mean of 2.6 years.

■ CSF total tau levels at baseline can aid prediction of subsequent neuronal degeneration as measured by using longitudinal changes in diffusion-tensor imaging metrics, and the results suggest that patients with increased CSF total tau levels might represent a subgroup of patients with MCI at risk for accelerated decline in WM integrity and possibly at greater risk of developing Alzheimer disease.

Implication for Patient Care

■ Identification of a subgroup of patients with MCI who are at possibly greater risk for dementia is important with regard to information provided to the patient and next of kin, treatment planning, and early intervention and medication.

memory impairment lasting 6 months or longer, preserved general intellectual function, none or very mild problems with activities of daily living, and Global Deterioration Scale (15) score of 2 or 3, as determined by clinical interview and screening tests. The screening tests consisted of parameters 13–20 (memory, disorientation, abstract thinking, visuospatial function, language, sensory aphasia, visual agnosia, and apraxia) from the Stepwise Comparative Status Analysis, or STEP (16), verbal fluency, interference, and number-letter elements from I-Flex, which is a short form of the executive interview (17). Also included were elements from the Neurobehavioral Cognitive Status Examination (18), Clinical Dementia Rating (19), and Mini-Mental State Examination (MMSE [20]). Patients with MMSE score of 28 or higher, Stepwise Comparative Status Analysis score of 0, I-Flex score of 1 or lower, and a score of 0.5 in a maximum of one Clinical Dementia Rating domain were classified as having a Global Deterioration Scale score of 2. Patients with an MMSE score of 26 or higher, a Stepwise Comparative Status Analysis score of 1 or lower, an I-Flex score of 2 or lower, and a score of 0.5 in more than one Clinical Dementia Rating domain were classified as having a Global Deterioration Scale score of 3. One patient with an MMSE score of 23 was included in the group with a Global Deterioration Scale score of 3 because the participant was self supporting and employed.

Criteria for exclusion were established psychiatric disorder, anoxic brain damage, cancer, drug abuse, or cognitive symptoms related to solvent exposure. Between baseline and follow-up, seven control subjects objected to reexamination, and one died of unrelated causes. Four patients with MCI objected to reexamination, one died of unrelated causes, and five were excluded because of definite other diagnoses. Fourteen participants were excluded on the basis of missing CSF data or missing or suboptimal data from diffusion-tensor imaging. This left 55 participants with complete data

sets for both baseline and follow-up at the time of study. Patients and control subjects were assessed and evaluated clinically by two authors (V.S. and P.S., with 2 and 3 years of experience, respectively). Neuropsychological testing was performed by one author (R.G., with 3 years of experience).

Lumbar Puncture and Laboratory Analyses

Patients underwent lumbar puncture as part of the clinical evaluation; it was not available for the control subjects. The CSF samples were examined for total tau levels with commercially available kits (Innogenetics, Ghent, Belgium). The age-dependent criteria for pathologic values were based on a large sample of healthy control subjects and were as follows: total tau of 300 ng/L or higher for age younger than 50 years, total tau of 450 ng/L or higher for age 50–69 years, and total tau of 500 ng/L or higher for age older than 70 years (21). The 0.90 fractile was estimated to establish reference values for CSF tau. CSF analyses were performed at Akershus University Hospital, Lørenskog, Norway. The MCI group was categorized with regard to CSF total tau levels into MCI low-tau and MCI high-tau groups.

Imaging Acquisition

For practical reasons, two magnetic resonance (MR) imaging devices were used. At baseline, 13 patients and eight control subjects underwent MR imaging at site I; and 26 patients and eight control subjects, at site II. All participants had imaging at site II at follow-up. Diffusion-tensor images were acquired by using two-dimensional spin-echo echo-planar imaging sequences, with diffusion weighting applied along 12 noncolinear directions. At site I, imaging unit A (Symphony; Siemens Medical Solutions, Erlangen, Germany), a 1.5-T MR imaging device with software version 4VA25A (Siemens Medical Solutions) was used with the following parameters: repetition time msec/echo time msec, 4300/131; b value, 700 sec/mm^2; number of axial sections, 19; section thickness, 5 mm; spacing, 1.5 mm;

matrix, 128 × 128; and in-plane resolution, 1.8 × 1.8 mm. The sequence was repeated twice, and two images with a b value of 0 sec/mm^2 were obtained per imaging session. At site II, imaging unit B (Espree; Siemens Medical Solutions), a 1.5-T MR imaging device with software version 4VB13A (Siemens Medical Solutions) was used with the following parameters: 6100/117; b value, 750 sec/mm^2; number of axial sections, 30; section thickness, 3 mm; spacing, 0.9 mm; matrix, 192 × 192; and in-plane resolution, 1.2 × 1.2 mm. The sequence was repeated five times, and five images with a b value of 0 sec/mm^2 were obtained per imaging session. Mean duration between MR image acquisitions at baseline and at follow-up did not differ significantly among groups (control subjects, 2.68 years ± 0.64; MCI low-tau group, 2.56 years ± 0.47; MCI high-tau group, 2.61 years ± 0.61).

Diffusion-Tensor Imaging

Image data were processed and analyzed by using tools from the Oxford Centre for Functional MRI of the Brain Software Library (FSL; *http://www.fmrib.ox.ac.uk/fsl*). Following the standard tract-based spatial statistics processing stream, maps of fractional anisotropy (FA), mean diffusivity (D_M), D_R, and axial diffusivity (D_A) were calculated from the fitted diffusion tensors after eddy-current corrections and brain extraction (22). We analyzed images from both times by using tract-based spatial statistics (22) but applied a modified processing scheme designed to optimize intrasubject registration to account for change of MR imaging unit, varying head placement, and unit drift between sessions (Fig 1). We used a procedure as described by Engvig et al (23) in which a base FA map is created, representing an unbiased halfway point between the two times for each participant. Diffusion-tensor imaging maps from both times aligned to the base FA map were used to create skeletonized images at both baseline and follow-up. One author (I.K.A., with 4 years of experience) processed and analyzed all images.
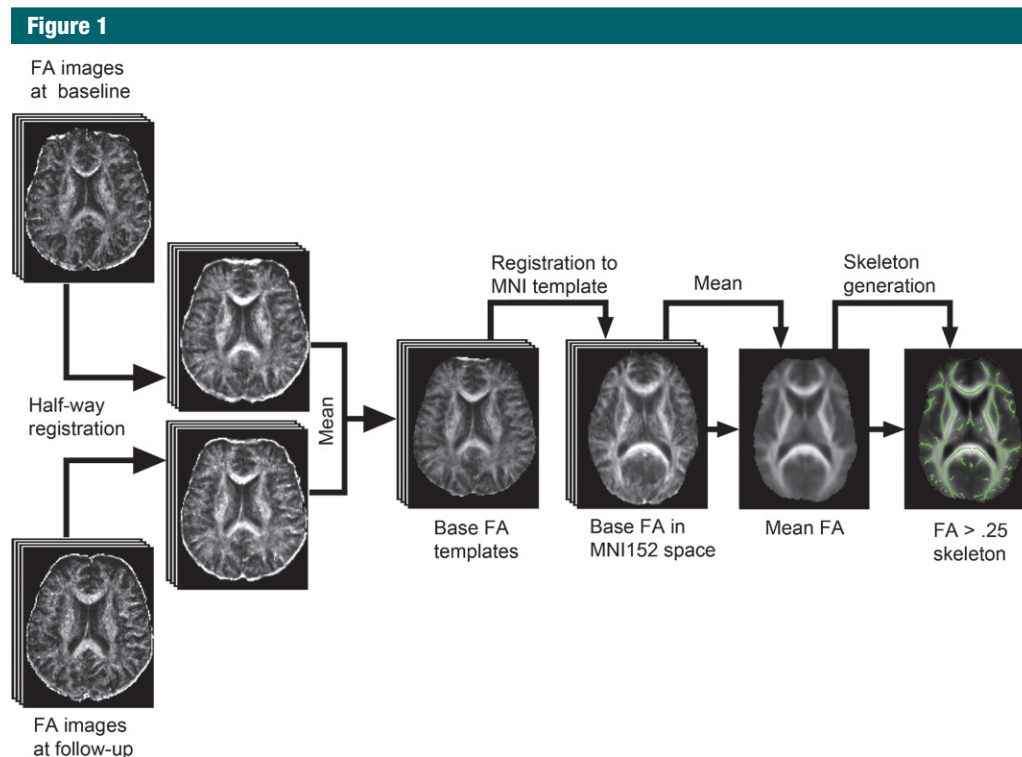
Figure 1

Figure 1: Simplified schematic representation of the half-way registration procedure and the generation of the common WM skeleton. *MNI* = Montreal Neurological Institute.

Statistical Analysis

A software package (SPSS, version 19.0; SPSS, Chicago, Ill) was used for comparisons of clinical and demographic variables: The χ^2 and Fisher exact tests were used to examine the differences in categorical variables, and one-way analysis of variance was used to examine the differences in continuous variables. The statistical analyses were performed by one author (I.A., with 4 years of experience).

Exploratory whole-brain voxel-wise analyses on all diffusion-tensor imaging indexes were performed between groups at both baseline and follow-up. Permutation-based nonparametric cluster inference (Randomize, a part of the FSL software suite) (24) was used, with controlling for effects of the imaging unit, sex, and age. A total of 5000 permutations were performed, and the results were corrected for multiple comparisons across space by threshold-free cluster enhancement (25). The threshold level

for a significant difference was set at $P < .05$ (corrected).

On the basis of the hypothesis that the MCI group would have more intense neuronal degeneration over time than would control subjects and that the diffusion-tensor imaging differences at follow-up would in part reflect this degeneration, we created binary masks from the voxels where MCI was significantly different (ie, lower FA and higher D_R) from those of control subjects at follow-up. We extracted the mean FA and D_R for all participants from both times in the voxels overlapping these regions of interest. Because D_A did not show significant group differences at follow-up (see below) and D_M was almost perfectly correlated with D_R ($r = 0.995$), these were omitted from further analysis.

Linear mixed-model between-group within-subject analysis (on the basis of restricted maximum likelihood) was conducted to examine effect of group on rate of change over

time in FA and D_R. Sex was entered as a covariate of no interest, and age and imaging site were entered as time-varying covariates of no interest. We first examined rate of change between the MCI group as a whole versus control subjects; next, we extended the analyses by comparing rate of change between the MCI subgroups (MCI high-tau group vs MCI low-tau group) and between each of these subgroups and the control subjects.

To characterize the effects according to WM region, we created binary masks that were based on the Johns Hopkins University International Consortium of Brain Mapping diffusion-tensor imaging-81 WM labels atlas (26) and Johns Hopkins University WM tractography atlas (27), with a probability threshold of 5% chosen to accommodate variation in WM structure. The intersections between the tract-based spatial statistics WM skeleton and anatomic masks were used for the regional labeling of the effects (Fig 2).
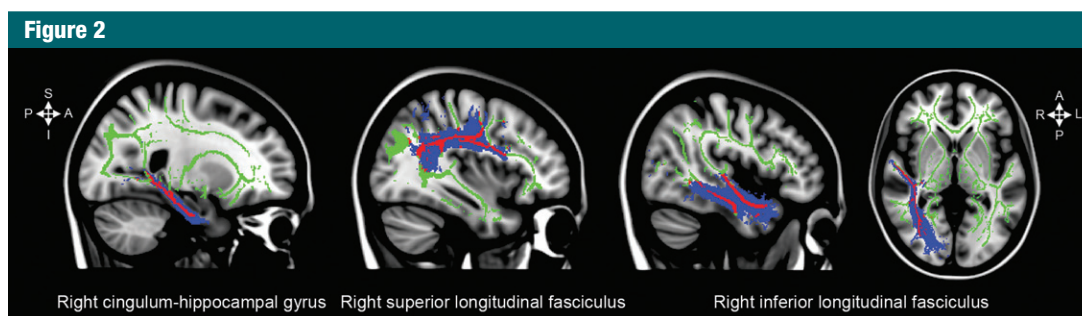
Figure 2

Right cingulum-hippocampal gyrus   Right superior longitudinal fasciculus   Right inferior longitudinal fasciculus

Figure 2:   Selected regions of interest superimposed on the mean WM skeleton template (green). Binary masks based on the Johns Hopkins University WM atlases (26,27) are shown in blue. Mean diffusion-tensor imaging values were extracted from the intersections between these binary masks and the mean WM skeleton voxels, shown in red. A = anterior, L = left, P = posterior, R = right.

The following regions and tracts were chosen: corpus callosum (genu, body, splenium), anterior thalamic radiation, cingulum in the cingulate area, hippocampal area of the cingulum, corticospinal tract, inferior and superior longitudinal fasciculi, inferior occipitofrontal fasciculus, uncinate fasciculus, forceps major, and forceps minor.

Results

The MCI and control groups did not differ significantly for age, sex, or education. Analysis of the CSF samples revealed that nine patients had pathologic CSF total tau levels, leaving nine patients in the MCI high-tau group and 30 patients in the MCI low-tau group. After we classified subjects in the MCI group, the MCI high-tau and MCI low-tau groups and the control group did not differ significantly for age, sex, or education. MMSE scores did not differ significantly between the MCI high-tau and MCI low-tau groups. Demographic and clinical characteristics are summarized in Table 1.

The cross-sectional analyses revealed that MCI had significantly ($P <$ .05, corrected) lower FA and higher D_R, D_M, and D_A in widespread areas compared with control subjects at both times (Figs 3, 4), with the exception of no significant group differences for D_A at follow-up. Table 2 provides details of the regional distribution of effects at follow-up.

The differences in rate of change between MCI and control subjects for FA were not significant ($F = 2.63$; $df =$ 1, 52.06; $P = .11$), but significant differences were found between the MCI and control groups in rate of D_R change: The patients with MCI showed a higher rate of increase in D_R over time than did control subjects ($F = 5.48$; $df = 1$, 53.2; $P = .023$).

The MCI high-tau group showed a significantly higher rate of FA decrease ($F = 4.85$; $df = 1$, 21.75; $P = .038$) and a higher rate of D_R increase ($F = 6.60$; $df = 1$, 22.01; $P = .018$) than did control subjects. In comparing the rate of change between the MCI high-tau and MCI low-tau groups or between the MCI

low-tau and control groups, no significant differences were seen, but a trend of progressively more intense WM degeneration across groups emerged. The MCI high-tau group displayed an almost significantly higher rate of change than did the MCI low-tau group for FA ($F = 3.47$; $df = 1$, 36.24; $P = .071$) and for D_R ($F = 3.95$; $df = 1$, 36.63; $P = .054$), and the MCI low-tau group had an almost significantly higher rate of D_R change than did control subjects ($F = 3.85$; $df = 1$, 44.00; $P = .056$).

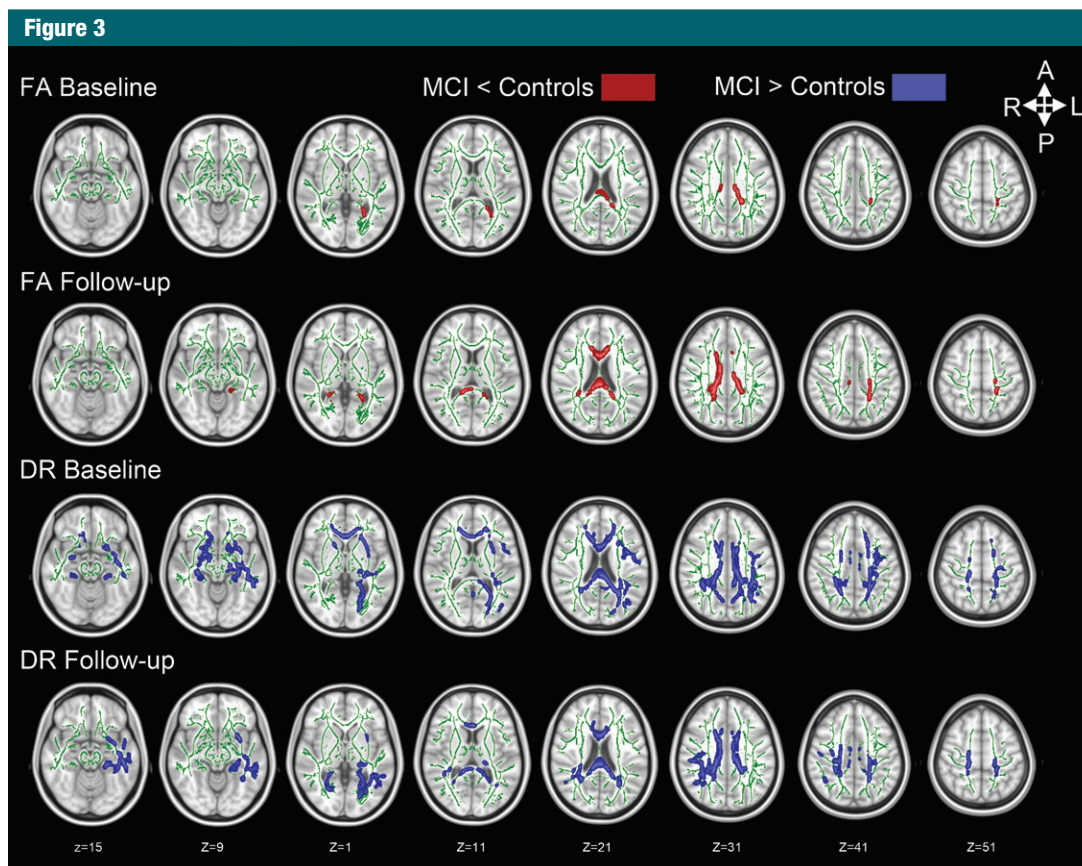Having established the MCI high-tau group as the subgroup with the most intense WM degeneration, we extended

Table 1

Demographic and Clinical Characteristics and CSF Biomarker Levels according to Group

Variable	MCI High-Tau Group ($n = 9$)	MCI Low-Tau Group ($n = 30$)	Control Group ($n = 16$)
Sex			
No. of men	6	14	6
No. of women	3	16	10
Age (y)*	64.11 (45–76)	58.50 (45–77)	61.69 (46–74)
No. of years of education†	12.22 (7–18)	11.85 (7–18)	11.53 (8–16)
MMSE score*	27.22 (25–29)	27.90 (23–30)	…
Global Deterioration Scale			
No. with score 1	0	0	16
No. with score 2	1	8	0
No. with score 3	8	22	0
Total tau level (ng/L)*	660 (300–1399)	265 (70–430)	…
Aβ42 level (ng/L)*	718 (505–1110)	930 (401–1300)	…

Note.—No significant group differences were observed (except for expected differences in Global Deterioration Scale and CSF measures).

* Data are means, and numbers in parentheses are ranges.

† Numbers in parentheses are ranges.

Figure 3: Regions with reduced WM integrity (decreased FA in red and increased D_R *[DR]* in blue) in patients with MCI compared with control subjects at baseline and follow-up (threshold-free cluster enhancement–corrected for multiple comparisons at $P < .05$). The effects are superimposed on axial sections of the mean WM skeleton template in Montreal Neurological Institute space displayed in green and are filled for ease of viewing. A = anterior, L = left, P = posterior, R = right, Z = Montreal Neurological Institute coordinates of the section through the z-axis.

the analysis further, examining in which WM tracts the effects were strongest. WM tracts displaying significant interactions between groups (MCI tau vs control groups) and time (Fig 2) were the hippocampal area of the cingulum ($F = 6.69$; $df = 1, 22.13$; $P = .017$), right inferior longitudinal fasciculus ($F = 5.01$; $df = 1, 22.33$; $P = .035$), and the right superior longitudinal fasciculus ($F = 4.35$; $df = 1, 24.09$; $P = .048$) for D_R. When the same tracts were examined for FA, no comparison reached a significant difference.

Discussion

The results of the present study suggest that longitudinal changes in WM integrity may be related to intensity of neuronal degeneration as indexed by using pathologic CSF total tau levels. Patients with MCI who had pathologic levels of CSF total tau at baseline displayed greater subsequent declines in FA and greater increases in D_R compared with control subjects. This finding indicates the existence of a subgroup of patients with MCI who have more intense neuronal degeneration and concurrent accelerated reductions in WM integrity. The findings support the CSF total tau level as an important early biomarker for predicting rate of disease progress and outcome.

The current findings extend previously reported cross-sectional results in an overlapping sample. With the use of a manually placed region of interest, Stenset et al (11) found reduced WM integrity in posterior cingulum fibers when comparing the MCI high-tau group with the control group. The results from the present study indicate that the previously reported cross-sectional differences between MCI high-tau and control groups were not merely preexisting differences between the groups but might reflect ongoing degenerative processes. The results thus demonstrate that pathologic CSF total tau levels can be used to distinguish patients with MCI who have ongoing WM degeneration from patients without this degeneration. In addition, the region-of-interest analyses combined with longitudinal data revealed
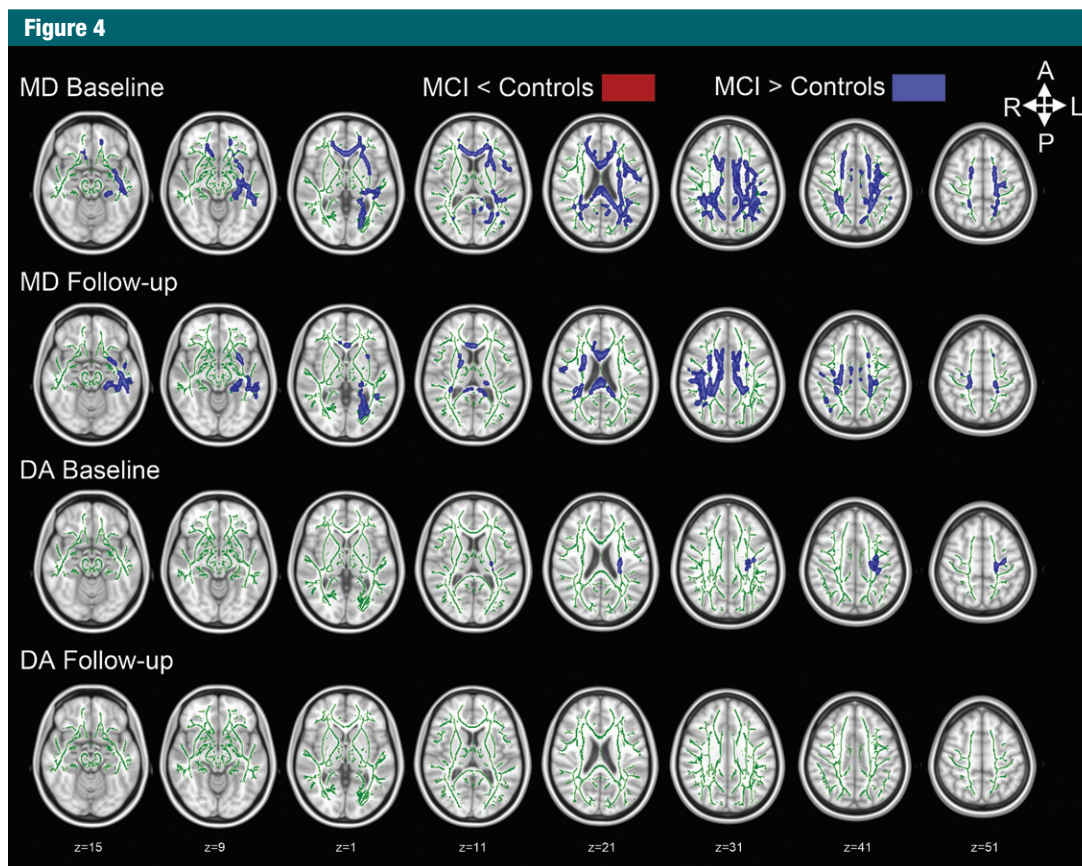
Figure 4: Regions with reduced WM integrity (increased D_M [MD] or D_A and D_R in blue) in patients with MCI compared with control subjects at baseline and follow-up (threshold-free cluster enhancement–corrected for multiple comparisons at $P < .05$). The effects are superimposed on axial sections of the mean WM skeleton template in Montreal Neurologic Institute space displayed in green and are filled for ease of viewing. A = anterior, L = left, P = posterior, R = right, Z = Montreal Neurological Institute coordinates of the section through the z-axis.

relations between pathologic CSF total tau level and WM degeneration in areas outside the cingulum area, including the right inferior and superior longitudinal fasciculus.

The present findings may help clarify previous longitudinal findings of no significant differences in WM change between MCI and control groups. Researchers in two longitudinal studies (9,10) failed to detect differences in change in WM integrity among patients with MCI, patients with AD, and control subjects. The lack of differences in WM change in one study (9) might be partially explained by the relatively short follow-up period. Teipel et al (10) did use a longer follow-up, and although their results show no

significant differences in change across groups on FA measures, the authors omitted reporting other diffusion-tensor imaging measures. However, these former studies did not include CSF biomarkers; group differences might have been detected if the analyses had been restricted to patients with pathologic CSF total tau levels because the present results indicate that the most intense WM degeneration is a characteristic only of a subgroup of patients with MCI.

Investigators in several previous studies detected differences between patients with MCI or AD and control subjects in diffusion parameters at baseline. Cross-sectional comparisons probably reflect years of accumulated

WM damage, amplifying group differences. Alternatively, low WM integrity may constitute a risk factor, which, combined with other risk factors (eg, increased total tau levels), may lead to MCI and AD. Longitudinal studies are necessary to solve such issues. Results of the present study suggest that reduced WM integrity is not merely a preexisting vulnerability factor toward developing MCI or AD but reflects characteristics of disease progression in patients who also have pathologic CSF total tau levels. Thus, longitudinal designs may have higher sensitivity to differences in WM change between patients and control subjects, but this seems to be true for a subgroup of patients only. This observation also

Table 2

Regional Distribution of Effects at Follow-up

Region	Total No. of Voxels	No. of Significant Voxels*	
		Lower FA in MCI vs Control Groups	Higher D_R in MCI vs Control Groups
Corpus callosum			
Genu	1789	95 (5)	270 (15)
Body	3200	1726 (54)	2223 (69)
Splenium	2445	919 (38)	1190 (49)
Anterior thalamic radiation			
Left	5812	60 (1)	263 (5)
Right	4666	8 (0)	22 (0)
Cingulum in cingulate area			
Left	996	70 (7)	254 (26)
Right	1195	211 (18)	418 (35)
Hippocampal area of cingulum			
Left	1308	135 (10)	706 (54)
Right	1131	65 (6)	116 (10)
Corticospinal tract			
Left	3390	222 (7)	399 (12)
Right	3522	0	622 (18)
Forceps			
Major	5318	302 (6)	676 (13)
Minor	5503	74 (1)	261 (5)
Inferior occipito frontal fasciculus			
Left	7757	0	808 (10)
Right	8318	43 (1)	277 (3)
Inferior longitudinal fasciculus			
Left	6279	0	1312 (21)
Right	4958	4 (0)	108 (2)
Superior longitudinal fasciculus			
Left	8924	27 (0)	809 (9)
Right	8391	13 (0)	1277 (15)
Uncinate fasciculus			
Left	3586	0	430 (12)
Right	2446	0	0

Note.—Data are number of skeleton voxels overlapping each tract or region of interest, displaying significantly lower FA and higher D_R in patients with MCI versus healthy control subjects ($P < .05$, threshold-free cluster enhancement–corrected for multiple comparisons).

* Numbers in parentheses are percentages.

were not biased (11,12). In addition, at present it is not well documented how neurodegeneration in the MCI high–total tau group relates to mechanisms of incipient AD disease. Finally, the sample size was limited with regard to the number of patients with pathologic levels of CSF total tau biomarkers. Because we were primarily interested in early mechanisms for AD, we focused on a heterogeneous group of patients with MCI, including patients manifesting both objective and subjective memory problems. Consequently, a lower proportion of patients had pathologic CSF total tau levels than might have been expected in a group consisting solely of, for instance, patients with amnestic MCI.

In conclusion, the results of the present study show that WM degeneration characterizes a subgroup of patients with MCI and is related to levels of CSF tau. This finding demonstrates the benefits of combining neuroimaging and established CSF biomarkers in research on early stages of the disease. An important task in future research will be to test disease progression in the subgroups of patients.

demonstrates the benefits of combining different methods and approaches to understand the mechanisms involved in MCI and AD. It will be an important task for further researchers to study the long-term outcome and conversion rate for this subgroup of patients.

The present study had limitations. First, the use of different MR imaging units and acquisition protocols could have potentially introduced biases. However, because we applied statistical control for the effect of imaging unit site in all analyses and the number of patients and control subjects examined with each device at baseline was almost equal, we do not believe that this has contributed to the observed effects. Further, previous studies on partially overlapping samples have shown that data collected from the imaging units are comparable and the results

References

1. Shaw LM, Vanderstichele H, Knapik-Czajka M, et al. Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. Ann Neurol 2009; 65(4):403–413.

2. Buée L, Bussière T, Buée-Scherrer V, Delacourte A, Hof PR. Tau protein isoforms, phosphorylation and role in neurodegenerative disorders. Brain Res Brain Res Rev 2000;33(1):95–130.

3. Zetterberg H, Hietala MA, Jonsson M, et al. Neurochemical aftermath of amateur boxing. Arch Neurol 2006;63(9):1277–1280.

4. Van Everbroeck B, Quoilin S, Boons J, Martin JJ, Cras P. A prospective study of CSF markers in 250 patients with possible Creutzfeldt-Jakob disease. J Neurol Neurosurg Psychiatry 2003;74(9):1210–1214.

5. Hesse C, Rosengren L, Andreasen N, et al. Transient increase in total tau but not phospho-tau in human cerebrospinal fluid after acute stroke. Neurosci Lett 2001;297(3):187–190.

6. Brun A, Englund E. A white matter disorder in dementia of the Alzheimer type: a pathoanatomical study. Ann Neurol 1986;19(3):253–262.

7. Le Bihan D, Mangin JF, Poupon C, et al. Diffusion tensor imaging: concepts and applications. J Magn Reson Imaging 2001; 13(4):534–546.

8. Sexton CE, Kalu UG, Filippini N, Mackay CE, Ebmeier KP. A meta-analysis of diffusion tensor imaging in mild cognitive impairment and Alzheimer's disease. Neurobiol Aging 2011;32(12):2322.e5–e18.

9. Mielke MM, Kozauer NA, Chan KCG, et al. Regionally-specific diffusion tensor imaging in mild cognitive impairment and Alzheimer's disease. Neuroimage 2009;46(1): 47–55.

10. Teipel SJ, Meindl T, Wagner M, et al. Longitudinal changes in fiber tract integrity in healthy aging and mild cognitive impairment: a DTI follow-up study. J Alzheimers Dis 2010;22(2):507–522.

11. Stenset V, Bjørnerud A, Fjell AM, et al. Cingulum fiber diffusivity and CSF T-tau in patients with subjective and mild cognitive impairment. Neurobiol Aging 2011;32(4): 581–589.

12. Walhovd KB, Fjell AM, Amlien I, et al. Multimodal imaging in mild cognitive impairment: metabolism, morphometry and diffusion of the temporal-parietal memory network. Neuroimage 2009;45(1):215–223.

13. Fjell AM, Walhovd KB, Amlien I, et al. Morphometric changes in the episodic memory network and tau pathologic features correlate with memory performance in patients with mild cognitive impairment. AJNR Am J Neuroradiol 2008;29(6):1183–1189.

14. Grambaite R, Stenset V, Reinvang I, Walhovd KB, Fjell AM, Fladby T. White matter diffusivity predicts memory in patients with subjective and mild cognitive impairment and normal CSF total tau levels. J Int Neuropsychol Soc 2010;16(1):58–69.

15. Reisberg B, Ferris SH, de Leon MJ, Crook T. Global Deterioration Scale (GDS). Psychopharmacol Bull 1988;24(4):661–663.

16. Wallin A, Edman A, Blennow K, et al. Stepwise comparative status analysis (STEP): a tool for identification of regional brain syndromes in dementia. J Geriatr Psychiatry Neurol 1996;9(4):185–199.

17. Royall DR, Mahurin RK, Gray KF. Bedside assessment of executive cognitive impairment: the executive interview. J Am Geriatr Soc 1992;40(12):1221–1226.

18. Kiernan RJ, Mueller J, Langston JW, Van Dyke C. The Neurobehavioral Cognitive Status Examination: a brief but quantitative approach to cognitive assessment. Ann Intern Med 1987;107(4):481–485.

19. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology 1993;43(11):2412–2414.

20. 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(3): 189–198.

21. Sjögren M, Vanderstichele H, Agren H, et al. Tau and Abeta42 in cerebrospinal fluid from healthy adults 21-93 years of age: establishment of reference values. Clin Chem 2001; 47(10):1776–1781.

22. Smith SM, Jenkinson M, Johansen-Berg H, et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage 2006;31(4):1487–1505.

23. Engvig A, Fjell AM, Westlye LT, et al. Memory training impacts short-term changes in aging white matter: a longitudinal diffusion tensor imaging study. Hum Brain Mapp 2012:13(10):2390–2406.

24. Nichols TE, Holmes AP. Nonparametric permutation tests for functional neuroimaging: a primer with examples. Hum Brain Mapp 2002;15(1):1–25.

25. Smith SM, Nichols TE. Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. Neuroimage 2009;44(1):83–98.

26. Mori S, Oishi K, Jiang H, et al. Stereotaxic white matter atlas based on diffusion tensor imaging in an ICBM template. Neuroimage 2008;40(2):570–582.

27. Hua K, Zhang J, Wakana S, et al. Tract probability maps in stereotaxic spaces: analyses of white matter anatomy and tract-specific quantification. Neuroimage 2008;39(1):336–347.