ON-LINE APPENDIX SECTION 1: IMAGE ACQUISITION

The MR protocol included 3D T1-weighted imaging for anatomic reference by using an MPRAGE sequence with the following parameters: TR/TI/TE = 2200/1100/2.26 ms, FOV = 256 × 265 mm^2, matrix size = 256 × 265, a generalized autocalibrating partially parallel acquisition (GRAPPA) factor of two, 160 sections, section thickness = 1 mm, voxel size = 1 × 1 × 1 mm^3, scan duration = 3 minutes, 29 seconds. To outline WM lesions, we performed a FLAIR sequence with a BLADE (Siemens) trajectory with the following parameters: TR/TI/TE = 9013/2500/134 ms, 3 minutes, 2 seconds, 0.7 × 0.7 × 5 mm^3, FOV = 220 × 220 mm^2, matrix size = 320 × 320, a GRAPPA factor of two, 3 minutes 2 seconds, section thickness = 5 mm, voxel size = 0.7 × 0.7 × 5 mm^3, scan duration = 3:02 minutes. Diffusion imaging was performed with 3 b-values (0, 1000, 2000 s/mm^2) along 30 diffusion-encoding directions by using single-shot twice-refocused EPI. Other imaging parameters were the following: TR/TE = 5900/96 ms, averages = 11 for b=0 and 2 for b=1000, 2000 s/mm^2, FOV = 222 × 222 mm^2, matrix size = 82 × 82, a GRAPPA factor of two, 45 oblique sections, section thickness = 2.7 mm, voxel size = 2.7 × 2.7 × 2.7 mm^3, scan duration = 13 minutes, 47 seconds.

ON-LINE APPENDIX SECTION 2: IMAGE PROCESSING AND ANALYSIS

Matlab R2009b (MathWorks, Natick, Massachusetts) was used for checking image quality and motion correction and producing the DKI parametric maps. 3D motion correction was performed on the diffusion-weighted images by using SPM8 (Wellcome Trust Centre for Neuroimaging, London, UK) followed by spatial smoothing by using a Gaussian filter with a full width at half maximum of 3.375 mm. The DKI processing algorithm[1] provided parametric maps of the standard diffusivity metrics of mean diffusivity (MD), axial diffusivity ($D_{\parallel}$), radial diffusivity ($D_{\perp}$), and fractional anisotropy (FA), as well as the additional kurtosis metrics of mean kurtosis (MK), axial kurtosis, ($K_{\parallel}$) and radial kurtosis ($R_{\perp}$). These maps, along with the corresponding tensors, were then used to derive the WMTI maps.

Both voxelwise analysis by using the standard procedure of tract-based spatial statistics[2,3] and region-of-interest analysis of the corpus callosum were performed. Using FSL (Analysis Group, FMRIB), we nonlinearly registered the individual FA maps to the FMRIB58 FA template and resampled them to the 1 × 1 × 1 mm^3 Montreal Neurological Institute 152 space. All other parametric maps underwent the same transformations for subsequent processing. A mean FA map over all subjects was created. ROIs of the genu, body, and splenium of the corpus callosum were drawn on the FA template on the basis of the John Hopkins University WM label atlas.[4] The tract skeleton was thresholded to FA $\geq$ 0.4 to restrict further analysis to WM regions consisting of single-fiber orientations. Means and SDs over the callosal ROIs were extracted for each metric for subsequent statistical analyses. With TBSS, we created a mean FA skeleton, and all parametric maps (11 in total) of each subject were then projected onto this for further skeletonized voxelwise statistical analysis. The average values over the FA skeleton for each metric were also derived for statistical analysis.

ON-LINE APPENDIX SECTION 3: STATISTICAL ANALYSES

One-way analysis of variance and χ^2 tests were initially conducted to investigate differences in demographic and medical history information among NC and subjects with aMCI and AD. As presented in On-line Table 1, there were no statistically significant differences among the groups in demographic characteristics. While the average ages of the groups were not significantly different, age was included as a covariate in group difference analyses to address the different age ranges of each subject group and the age dependence of the diffusion metrics. Accordingly, the reported correlations with the CPS score used age-residualized WMTI metrics. On-line Table 1 also demonstrates that there were no significant differences among these groups in their medical history, including vascular comorbidities that may affect WM integrity.[5] We examined whether WM lesions were disproportionally present in our groups: A neuroradiologist (M.V.S.) blinded to subject diagnosis provided a Scheltens Scale score[6] by using the FLAIR image for each subject. Because the NC (12.33 ± 8.43) and subjects with aMCI (12.42 ± 8.25) and AD (13.85 ± 8.71) did not significantly differ on their total Scheltens Scale score [$F(2, 37)$ = 0.13, P = .88] or in the subscale scores for periventricular hyperintensities (data not reported here), no further analyses incorporating this variable were conducted.

First, we tested for differences between groups by using data from the TBSS and region-of-interest analyses. In the TBSS analysis, skeletonized voxelwise statistical analyses were performed across all voxels on the skeleton by using a permutation-based interference tool for nonparametric statistical thresholding (Randomize;FSL). Between-group comparisons of the standard diffusivity, kurtosis, and WMTI metrics (11 in total) within the skeleton were tested by using t tests, with subject age as a covariate. The number of permutations was set to 5000. The resulting statistical maps were thresholded (one-sided $P < .05$), with correction for multiple comparisons included by using the threshold-free cluster enhancement option.[7] Region-of-interest analysis was performed in Matlab R2009b to study the WMTI metrics in more detail. We used ANCOVA to compare subject groups (NC, aMCI, AD) for each regional metric, covarying for age. A separate analysis was conducted for each metric (AWF, D_{axon}, $D_{e,\parallel}$, and $D_{e,\perp}$) within each region of interest (4 in total). In each analysis, the region of interest was the dependent variable and the model included age and sex as a numeric factor and group membership as a classification factor. A Tukey-Kramer correction was performed for multiple group comparisons (NC versus aMCI, aMCI versus AD, and NC versus AD). Group comparisons were declared statistically significant at the two-sided 5% Tukey-corrected significance level. Additionally, to account for the fact that tests were conducted for multiple ROIs, P values remaining significant after Bonferroni correction for multiple ROIs were indicated. Second, we conducted area under the receiver operating characteristic curve and linear discriminant analyses to assess the diagnostic utility of each regional metric in differentiating each group. Last, in preparation for the correlation analyses, we regressed age on each WMTI metric. Spearman correlations of the age-residualized WMTI metrics of the regions of interest and CPS score were conducted by using the Statistical Package for the Social Sciences,

On-line Table 1: ANCOVA post hoc and AUC results of the standard diffusivity and kurtosis metrics of each corpus callosum ROI and the FA skeleton

		NC (n = 15)	aMCI (n = 12)	AD (n = 14)	NC vs aMCI		aMCI vs AD		NC vs AD	
	ROI	Mean ±SD	Mean ±SD	Mean ±SD	*P* Value	AUC	*P* Value	AUC	*P* Value	AUC
Standard diffusivity metrics										
MD	Genu	1.11 ± 0.08	1.22 ± 0.09	1.27 ± 0.18	.05	0.88	.38	0.63	<.01	0.87
	Body	1.15 ± 0.08	1.24 ± 0.09	1.28 ± 0.15	.10	0.82	.69	0.64	<.01	0.79
	Splenium	0.99 ± 0.07	1.07 ± 0.08	1.16 ± 0.16	.22	0.78	.02	0.77	<.01	0.90
	Skeleton	0.87 ± 0.05	0.91 ± 0.04	0.96 ± 0.10	.20	0.78	.03	0.77	<.01	0.88
$D_{\parallel}$	Genu	1.84 ± 0.09	1.94 ± 0.07	1.98 ± 0.17	.09	0.82	.61	0.61	<.01	0.82
	Body	1.87 ± 0.08	1.94 ± 0.09	1.94 ± 0.12	.17	0.76	1.00	0.51	.10	0.70
	Splenium	1.74 ± 0.09	1.80 ± 0.08	1.85 ± 0.11	.22	0.72	.39	0.67	<.01	0.81
	Skeleton	1.42 ± 0.05	1.46 ± 0.04	1.48 ± 0.07	.07	0.77	0.24	0.71	<.01	0.87
$D_{\perp}$	Genu	0.75 ± 0.08	0.86 ± 0.11	0.91 ± 0.20	0.05	0.88	.36	0.64	<.01	0.88
	Body	0.80 ± 0.08	0.90 ± 0.09	0.95 ± 0.18	.11	0.85	.33	0.66	<.01	0.82
	Splenium	0.62 ± 0.07	0.70 ± 0.08	0.81 ± 0.18	.27	0.79	<.01	0.82	<.01	0.91
	Skeleton	0.59 ± 0.05	0.64 ± 0.05	0.69 ± 0.12	.33	0.75	.02	0.78	.33	0.87
FA	Genu	0.39 ± 0.03	0.36 ± 0.04	0.35 ± 0.05	.16	0.77	.38	0.64	<.01	0.85
	Body	0.43 ± 0.03	0.40 ± 0.03	0.37 ± 0.06	.18	0.83	.14	0.67	<.01	0.84
	Splenium	0.54 ± 0.03	0.51 ± 0.04	0.46 ± 0.07	.47	0.77	<.01	0.86	<.01	0.93
	Skeleton	0.51 ± 0.03	0.49 ± 0.03	0.46 ± 0.06	.71	0.72	.02	0.80	<.01	0.86
Kurtosis metrics										
MK	Genu	0.91 ± 0.06	0.87 ± 0.07	0.84 ± 0.12	1.00	0.70	.55	0.64	.09	0.68
	Body	0.88 ± 0.07	0.86 ± 0.07	0.82 ± 0.11	1.00	0.68	.23	0.70	.09	0.72
	Splenium	0.99 ± 0.11	0.99 ± 0.07	0.91 ± 0.12	1.00	0.63	.08	0.79	.13	0.69
	Skeleton	1.00 ± 0.08	1.01 ± 0.06	0.95 ± 0.10	1.00	0.62	.15	0.74	.48	0.64
$K_{\parallel}$	Genu	0.60 ± 0.03	0.60 ± 0.02	0.59 ± 0.05	1.00	0.66	1.00	0.63	.94	0.56
	Body	0.55 ± 0.09	0.57 ± 0.07	0.58 ± 0.05	.91	0.68	1.00	0.53	.74	0.59
	Splenium	0.57 ± 0.06	0.59 ± 0.04	0.58 ± 0.04	.84	0.68	1.00	0.70	1.00	0.57
	Skeleton	0.69 ± 0.04	0.70 ± 0.03	0.69 ± 0.04	.54	0.71	1.00	0.63	1.00	0.60
$K_{\perp}$	Genu	1.40 ± 0.14	1.31 ± 0.16	1.26 ± 0.27	.81	0.71	.78	0.63	.07	0.70
	Body	1.43 ± 0.17	1.33 ± 0.16	1.23 ± 0.27	.64	0.73	.31	0.69	.01	0.78
	Splenium	1.62 ± 0.21	1.59 ± 0.16	1.39 ± 0.28	1.00	0.68	.03	0.81	.01	0.80
	Skeleton	1.43 ± 0.16	1.43 ± 0.12	1.31 ± 0.19	1.00	0.63	.10	0.77	.16	0.68

Note:—MD indicates mean diffusivity; $D_{\parallel}$, axial diffusivity; $D_{\perp}$, radial diffusivity; FA, fractional anisotrospy; MK, mean kurtosis; $K_{\parallel}$, axial kurtosis and $K_{\perp}$, radial kurtosis.

Version 19 (SPSS, Chicago, Illinois). A conservative Bonferroni-corrected significance value was set to $P < .05/48 = 0.001$ to minimize type 1 error from the multiple correlations among the 16 regional metrics of the 3 groups (ie, 48 comparisons).

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