Supplementary Table 1. Models of the diffusion parameters in WMC, parahippocampal and normal-appearing WM with all neuroimaging markers and including the APOE genotype as a variable.

Model 1	**WMC (subgroup with volume > 1% total WM volume, n = 95)**			
Parameters	MD (β; p-value)	DA (β; p-value)	DR (β; p-value)	FA (β; p-value)
Group (MCI)	0.01; 0.8758	0.03; 0.6721	-0.00; 0.9920	0.09; 0.3802
Group (AD)	0.18; 0.0514	0.14; 0.1317	*0.20; 0.0331*	-0.22; 0.1077
Age	0.04; 0.4161	0.02; 0.6485	0.05; 0.3107	-0.15; 0.0638
Gender (female)	0.02; 0.6687	0.01; 0.8442	0.03; 0.5656	-0.09; 0.2792
Education	0.06; 0.2429	0.04; 0.4547	0.07; 0.1719	-0.13; 0.0815
APOE4 (per allele)	***-0.23; 0.0039**	***-0.25; 0.0022**	*-0.22; 0.0071*	-0.05; 0.6673
Cortical thickness	0.04; 0.5646	-0.01; 0.8686	0.06; 0.3212	***-0.27; 0.0034**
Hippocampal vol.	0.11; 0.1389	0.10; 0.1651	0.11; 0.1377	-0.13; 0.2357
Ventricular volume	****0.57; <0.0001**	****0.60; <0.0001**	****0.54; <0.0001**	0.09; 0.2860
Volume of WMC	*-0.21; 0.0162*	*-0.20; 0.0195*	*-0.22; 0.0150*	-0.06; 0.6055
Total WM volume	*-0.12; 0.0290*	*-0.12; 0.0352*	*-0.12; 0.0304*	0.09; 0.2553
Norm. properties	****0.58; <0.0001**	****0.57; <0.0001**	****0.59; <0.0001**	****0.54; <0.0001**
Translation motion	***0.30; 0.0031**	*0.22; 0.0259*	***0.34; 0.0010**	***-0.46; 0.0020**
Rotation motion	*-0.27; 0.0053*	*-0.21; 0.0273*	***-0.30; 0.0025**	*0.31; 0.0273*

Model 2	**Parahippocampal WM (all, n = 169)**			
Parameters	MD (β; p-value)	DA (β; p-value)	DR (β; p-value)	FA (β; p-value)
Group (MCI)	-0.06; 0.5322	0.02; 0.8029	-0.09; 0.2743	0.13; 0.1244
Group (AD)	0.09; 0.5428	-0.03; 0.8377	0.14; 0.2970	-0.23; 0.0940
Age	0.03; 0.7199	-0.01; 0.9273	0.05; 0.5503	-0.10; 0.2164
Gender (female)	0.02; 0.8113	-0.04; 0.5837	0.05; 0.4932	*-0.15; 0.0365*
Education	0.10; 0.1641	0.05; 0.5570	0.12; 0.0784	*-0.13; 0.0441*
APOE4 (per allele)	0.14; 0.1976	0.06; 0.5995	0.17; 0.1010	-0.17; 0.0856
Cortical thickness	*-0.22; 0.0143*	-0.16; 0.1022	*-0.24; 0.0060*	*0.20; 0.0181*
Hippocampal vol.	*-0.25; 0.0184*	-0.22; 0.0555	*-0.25; 0.0146*	0.18; 0.0657
Ventricular volume	-0.01; 0.9290	-0.06; 0.5561	0.02; 0.8308	-0.03; 0.7256
Volume of WMC	0.11; 0.2120	0.11; 0.2669	0.11; 0.2163	-0.09; 0.3014
Total WM volume	-0.04; 0.6445	0.08; 0.3985	-0.09; 0.2316	***0.24; 0.0025**
Translation motion	-0.03; 0.8415	0.06; 0.6677	-0.07; 0.5776	0.14; 0.2762
Rotation motion	0.15; 0.2346	0.05; 0.7389	0.20; 0.1091	*-0.24; 0.0481*

Model 3	**Normal-appearing white matter (all, n = 169)**			
Parameters	MD (β; p-value)	DA (β; p-value)	DR (β; p-value)	FA (β; p-value)
Group (MCI)	0.06; 0.4806	0.13; 0.1583	0.02; 0.7726	0.07; 0.3592
Group (AD)	-0.03; 0.8115	-0.05; 0.7202	-0.02; 0.8723	0.02; 0.8967
Age	0.08; 0.2896	0.13; 0.1263	0.05; 0.4562	0.02; 0.8026

Gender (female)	0.03; 0.6492	0.03; 0.6882	0.03; 0.6496	-0.02; 0.8062
Education	0.12; 0.0654	0.11; 0.1330	0.12; 0.0566	-0.08; 0.2076
APOE4 (per allele)	0.01; 0.9015	0.02; 0.8180	0.01; 0.9524	0.01; 0.9120
Cortical thickness	-0.13; 0.1182	-0.13; 0.1328	-0.12; 0.1347	0.05; 0.5490
Hippocampal vol.	0.03; 0.7405	-0.08; 0.4598	0.08; 0.3840	-0.16; 0.0976
Ventricular volume	0.05; 0.5436	0.10; 0.2563	0.02; 0.7712	0.09; 0.2716
Volume of WMC	***0.39; <0.0001**	*0.23; 0.0123*	***0.45; <0.0001**	***-0.52; <0.0001**
Total WM volume	-0.14; 0.0545	-0.02; 0.7581	*-0.19; 0.0084*	***0.25; 0.0011**
Translation motion	-0.15; 0.2049	*-0.31; 0.0209*	-0.07; 0.5247	-0.21; 0.0861
Rotation motion	**0.41; 0.0006**	**0.48; 0.0002**	***0.35; 0.0018**	-0.14; 0.2327

All continuous variables were standardized prior to applying the model for easier comparison of parameter estimates (β). Uncorrected p-values are presented and significant associations with corrected $p < 0.05$ are bolded (*, ** and *** for corrected $p < 0.05$, 0.01 and 0.001 respectively). Associations with uncorrected $p < 0.05$ are italicized. (WMC, white matter changes; WM, white matter).

Supplementary Table 2. Models of the diffusion parameters in WMC, parahippocampal and normal-appearing WM with factors extracted from the neuroimaging markers and including APOE genotype as a variable.

Model 4	**WMC (subgroup with volume > 1% total WM volume, n = 95)**			
Parameters	MD (β; p-value)	DA (β; p-value)	DR (β; p-value)	FA (β; p-value)
Group (MCI)	0.01; 0.8554	0.04; 0.6554	0.00; 0.9987	0.11; 0.2653
Group (AD)	0.01; 0.9334	-0.04; 0.6964	0.04; 0.7248	-0.20; 0.1342
Age	-0.02; 0.7735	-0.02; 0.7109	-0.01; 0.8410	*-0.17; 0.0302*
Gender (female)	0.05; 0.4395	0.05; 0.4654	0.05; 0.4038	-0.14; 0.0738
Education	0.08; 0.1800	0.06; 0.3555	0.10; 0.1181	-0.12; 0.0972
APOE4 (per allele)	*-0.23; 0.0174*	*-0.26; 0.0099*	*-0.22; 0.0272*	-0.05; 0.6481
Factor 1	***-0.50; <0.0001**	***-0.51; <0.0001**	***-0.47; <0.0001**	-0.10; 0.2652
Factor 2	*-0.18; 0.0104*	***-0.24; 0.0011**	*-0.15; 0.0403*	****-0.33; 0.0002**
Norm. properties	***0.90; <0.0001**	***0.89; <0.0001**	***0.89; <0.0001**	***0.52; <0.0001**
Translation motion	0.19; 0.1113	0.12; 0.3212	0.24; 0.0538	***-0.43; 0.0034**
Rotation motion	-0.22; 0.0651	-0.16; 0.1868	*-0.25; 0.0348*	*0.29; 0.0382*

Model 5	**Parahippocampal WM (all, n = 169)**			
Parameters	MD (β; p-value)	DA (β; p-value)	DR (β; p-value)	FA (β; p-value)
Group (MCI)	-0.04; 0.6751	0.05; 0.6150	-0.08; 0.3498	0.13; 0.1225
Group (AD)	0.14; 0.3139	0.03; 0.8646	0.19; 0.1538	-0.25; 0.0568
Age	0.06; 0.4492	0.02; 0.7787	0.07; 0.3261	-0.12; 0.1045
Gender (female)	-0.01; 0.8748	-0.09; 0.2706	0.03; 0.6770	*-0.16; 0.0196*
Education	0.09; 0.1994	0.03; 0.6780	0.11; 0.0891	*-0.13; 0.0422*
APOE4 (per allele)	0.14; 0.1839	0.07; 0.5638	0.17; 0.0943	-0.18; 0.0860
Factor 1	***-0.28; 0.0014**	-0.11; 0.2343	****-0.35; <0.0001**	****0.43; <0.0001**
Factor 2	****-0.29; 0.0003**	*-0.21; 0.0160*	****-0.31; <0.0001**	****0.27; 0.0005**
Translation motion	0.02; 0.8464	0.12; 0.3942	-0.03; 0.8312	0.12; 0.3359
Rotation motion	0.12; 0.3403	0.01; 0.9335	0.17; 0.1624	-0.23; 0.0582

Model 6	**Normal-appearing white matter (all, n = 169)**			
Parameters	MD (β; p-value)	DA (β; p-value)	DR (β; p-value)	FA (β; p-value)
Group (MCI)	0.06; 0.4774	0.14; 0.1273	0.02; 0.7983	0.08; 0.3740
Group (AD)	-0.07; 0.6142	-0.05; 0.6984	-0.07; 0.5985	0.08; 0.5839
Age	0.13; 0.0882	0.14; 0.0706	0.11; 0.1245	-0.07; 0.3871
Gender (female)	0.05; 0.4553	0.02; 0.8078	0.06; 0.3455	-0.07; 0.3281
Education	0.09; 0.1890	0.09; 0.1968	0.08; 0.2172	-0.03; 0.6619
APOE4 (per allele)	0.02; 0.8789	0.03; 0.7936	0.01; 0.9306	0.01; 0.9459
Factor 1	****-0.41; <0.0001**	****-0.32; 0.0003**	****-0.43; <0.0001**	****0.37; <0.0001**
Factor 2	*-0.21; 0.0054*	*-0.22; 0.0056*	*-0.19; 0.0094*	0.09; 0.2389
Translation motion	-0.17; 0.1665	*-0.30; 0.0215*	-0.10; 0.4067	-0.17; 0.1848

Rotation motion	****0.42; 0.0005**	****0.48; 0.0002**	***0.37; 0.0017**	-0.17; 0.1947

All continuous variables were standardized prior to applying the model for easier comparison of parameter estimates (β). Uncorrected p-values are presented and significant associations with corrected $p < 0.05$ are bolded (*, ** and *** for corrected $p < 0.05$, 0.01 and 0.001 respectively). Associations with uncorrected $p < 0.05$ are italicized. (WMC, white matter changes; WM, white matter).

Supplementary Figure 1. Examples of automated WMC segmentation by FreeSurfer in controls and individuals with MCI and AD with a) a low volume of WMC approximating 1% of total WM volume and b) a high volume of WMC approximating 5% of total WM volume. The WMC segmentation is represented by light purple. The rest of the segmentation corresponds to the standard color table freely available on the FreeSurfer website, though the segmentation of the inferior lateral ventricles was modified to a deep purple color like the rest of the ventricles to avoid confusion with the WMC segmentation.

Supplementary Figure 2. Scatterplots ofvolume of WMC, total WM volume, ventricular volume, hippocampal volume, and AD signature cortical thickness displayed as a correlation matrix. Hippocampal, ventricular, and total WM volumes were normalized by the estimated total intracranial volume. The natural logarithm of the volume of WMC divided by the total WM volume was used. Pearson's correlation coefficients and their associated p-valuesare shown on opposite sides of the diagonal. (WMC, white matter changes; WM, white matter; eTIV, estimated total intracranial volume; AD: Alzheimer's disease)