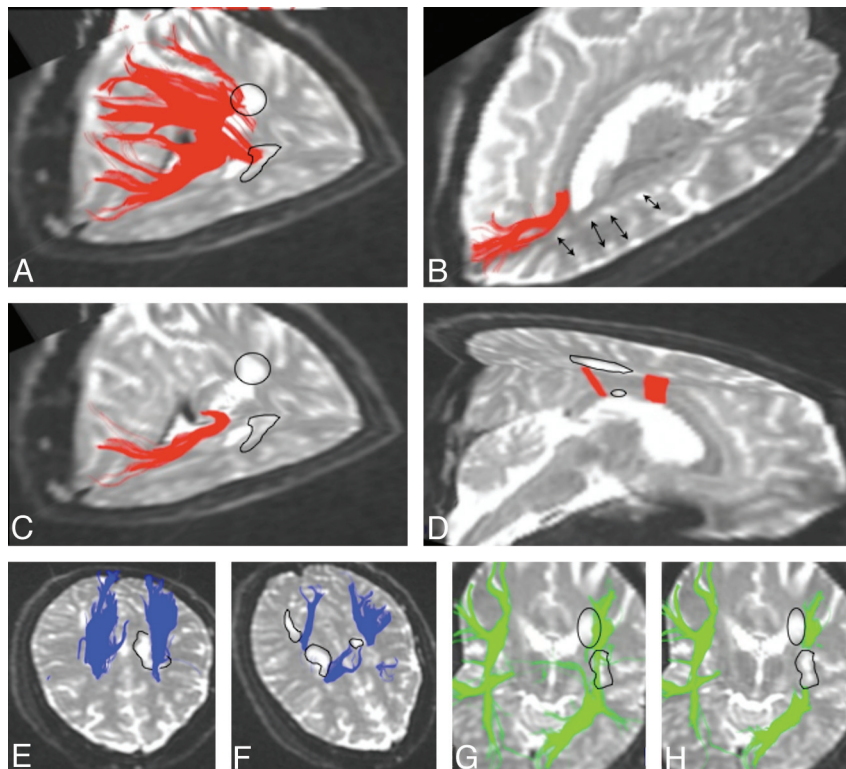**On-line Fig 1.** Overview of patient cohorts.

On-line Fig 2. White matter tracts passing through lesioned and nonlesioned white matter and NAWM with nonlesioned tracts only in patients with pediatric MS. *A*, Right posterosuperior view showing 3D reconstruction of interhemispheric (callosal) fibers passing through both lesioned and nonlesioned white matter in sagittal, coronal, and axial planes. T2 lesions are circled. *B*, Right anterosuperior view showing 3D reconstruction of fibers of the genu of the corpus callosum passing through NAWM in sagittal, coronal, and axial planes. T2 lesions are circled. *C*, Left posterosuperior view showing 3D reconstruction of fibers of the splenium of the corpus callosum passing through NAWM in sagittal and axial planes. T2 lesions are circled. *D*, Right inferior view showing 3D reconstruction of fibers of the anterior and posterior midbody of the corpus callosum passing through NAWM in sagittal and axial planes. Double arrowheads indicate T2 lesions. *E*, Superior view of the 3D reconstruction of projection fibers (right and left) passing through both lesioned and nonlesioned white matter in the axial plane. T2 lesions are circled. *F*, Superior view of 3D reconstruction of projection fibers passing through normal-appearing white matter in the axial plane. T2 lesions are circled. *G*, Left anterosuperior view showing 3D reconstruction of long-association fibers (superior longitudinal fascicle + uncinate fascicle + inferior fronto-occipital fascicle) passing through both lesioned and nonlesioned white matter in axial and coronal planes. T2 lesions are circled. *H*, Left anterosuperior view showing 3D reconstruction of LAFs (right and left) passing through NAWM in axial and coronal planes. T2 lesions are circled.

On-line Table: DTI measures of NAWM in pediatric CIS-baseline MRI

	MCIS			PCISWOE			PCISWE		
	Patients	Controls	P Value	Patients	Controls	P Value	Patients	Controls	P Value
Genu									
Mean ADC	0.84 ± 0.086	0.79 ± 0.11	.32	0.89 ± 0.093	0.87 ± 0.079	.64	0.98 ± 0.15	0.97 ± 0.069	.89
Mean FA	0.56 ± 0.032	0.56 ± 0.044	.71	0.56 ± 0.074	0.59 ± 0.056	.37	0.61 ± 0.094	0.61 ± 0.090	.92
Splenium									
Mean ADC	0.80 ± 0.096	0.77 ± 0.091	.46	0.88 ± 0.12	0.87 ± 0.10	.85	0.96 ± 0.081	0.94 ± 0.059	.49
Mean FA	0.61 ± 0.035	0.63 ± 0.055	.56	0.63 ± 0.045	0.66 ± 0.076	.41	0.63 ± 0.10	0.65 ± 0.065	.45
AMB									
Mean ADC	0.84 ± 0.13	0.84 ± 0.13	.97	0.91 ± 0.12	0.89 ± 0.11	.69	0.96 ± 0.13	1.0 ± 0.074	.34
Mean FA	0.55 ± 0.053	0.57 ± 0.047	.63	0.56 ± 0.036	0.57 ± 0.051	.72	0.54 ± 0.053	0.56 ± 0.061	.54
PMB									
Mean ADC	0.85 ± 0.16	0.84 ± 0.13	.86	0.92 ± 0.12	0.93 ± 0.11	.92	0.96 ± 0.13	0.99 ± 0.067	.45
Mean FA	0.57 ± 0.077	0.58 ± 0.043	.92	0.57 ± 0.041	0.59 ± 0.043	.15	0.55 ± 0.081	0.56 ± 0.043	.92
PLIC									
Mean ADC	0.70 ± 0.057	0.69 ± 0.060	.67	0.74 ± 0.063	0.71 ± 0.053	.071	0.75 ± 0.043	0.77 ± 0.020	.49
Mean FA	0.55 ± 0.033	0.56 ± 0.031	.48	0.57 ± 0.050	0.59 ± 0.051	.53	0.59 ± 0.066	0.59 ± 0.053	.75
CP									
Mean ADC	0.72 ± 0.054	0.70 ± 0.058	.43	0.75 ± 0.060	0.73 ± 0.049	.20	0.78 ± 0.034	0.79 ± 0.025	.086
Mean FA	0.56 ± 0.037	0.58 ± 0.031	.17	0.60 ± 0.052	0.61 ± 0.054	.70	0.60 ± 0.063	0.60 ± 0.059	.95
SLF									
Mean ADC	0.73 ± 0.059	0.71 ± 0.065	.43	0.77 ± 0.075	0.73 ± 0.054	.14	0.80 ± 0.063	0.78 ± 0.034	.34
Mean FA	0.48 ± 0.035	0.51 ± 0.039	.12	0.51 ± 0.054	0.54 ± 0.063	.25	0.52 ± 0.096	0.53 ± 0.062	.87
IFOF and UF									
Mean ADC	0.80 ± 0.071	0.77 ± 0.060	.22	0.84 ± 0.080	0.79 ± 0.078	.084	0.87 ± 0.038	0.85 ± 0.047	.45
Mean FA	0.46 ± 0.025	0.48 ± 0.039	.031[a]	0.44 ± 0.018	0.51 ± 0.029	.0012[a]	0.44 ± 0.069	0.46 ± 0.045	.23
All NAWM									
Mean ADC	0.78 ± 0.068	0.75 ± 0.070	.47	0.83 ± 0.084	0.80 ± 0.051	.36	0.86 ± 0.062	0.85 ± 0.035	.61
Mean FA	0.54 ± 0.024	0.56 ± 0.033	.11	0.55 ± 0.037	0.58 ± 0.040	.22	0.56 ± 0.052	0.57 ± 0.050	.85

Note:—AMB indicates anterior midbody; PMB, posterior midbody; SLF, superior longitudinal fascicle; UF, uncinate fascicle; IFOF, inferior fronto-occipital fascicle; CP, cerebral peduncle.
[a] Statistically significant.