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Appendix E1

Methods

MR Imaging Data Acquisition

The 3-T imaging protocol, performed by using the 32-channel coil (Siemens Healthcare, Forchheim, Germany), included acquisition of the following: (*a*) a structural scan with a three-dimensional magnetization-prepared rapid acquisition with multiple gradient echoes (repetition time msec/echo time msec, 2530/1.7, 3.6, 5.4, 7.3; inversion time msec, 1200; flip angle, 7°; field of view, 230 × 230 mm^2; resolution, 0.9 × 0.9 × 0.9 mm^3; bandwidth, 651 Hz/pixel) for cortical surface reconstruction and coregistration with 7-T data; and (*b*) a diffusion-weighted spin-echo echo-planar scan (9970/84; flip angle, 90°; field of view, 237 × 237 mm^2; resolution, 1.85 × 1.85 × 1.85 mm^3) by using 60 noncollinear diffusion gradients (*b* value, 700 sec/mm^2) and ten volumes without diffusion weighting (b_0 reference image).

The 7-T imaging protocol was performed by using a SC72 head gradient set (Siemens Healthcare) and a custom-built 32-channel phased array coil, and included acquisition of the following: (*a*) a multiecho two-dimensional fast low-angle shot T2*-weighted spoiled GRE pulse sequence (2210/6.44 + 3.32*n* [*n* = 0, …,11]; flip angle, 55°; two slabs that each consist of 40 sections to cover the supratentorial brain; field of view, 192 × 168 mm^2; in-plane resolution, 0.33 × 0.33 mm^2; 1-mm section thickness (25% gap); bandwidth, 335 Hz/pixel); (*b*) a single-echo two-dimensional fast low-angle shot T2*-weighted spoiled GRE pulse sequence (1700/21.8; the other parameters are identical to the multiecho two-dimensional fast low-angle shot T2* sequence); and (*c*) a T1-weighted three-dimensional magnetization-prepared rapid acquisition gradient echo (2600/3.26; inversion time msec, 1100; flip angle, 9°; field of view, 174 × 192 mm^2; resolution, 0.60 × 0.60 × 1.5 mm^3; bandwidth, 200 Hz/pixel) for coregistration purposes.

MR Imaging Data Processing

WM metrics.—

DTI images were preprocessed by using FMRIB software library's Diffusion Toolbox in FSL, which is included in the Tracts Constrained by Underlying Anatomy pipeline. Preprocessing steps included: 1) alignment of all images in the series to the first non-diffusion-weighted image using affine registration; 2) eddy currents correction; 3) fitting of the diffusion tensor model at each voxel. For each subject, we obtained maps of fractional anisotropy, axial diffusivity, and radial diffusivity. To investigate also the relationship between normal-appearing WM and cortical pathologic changes, WM lesion masks from single-echo T2* weighted images were coregistered to diffusion-weighted images by using boundary-based registration. Voxels in fractional anisotropy, axial diffusivity, and radial diffusivity maps that colocalized with WM lesions were masked to extract normal-appearing WM DTI metrics.

To assess pathologic changes along WM tracts, with and without WM lesions, four tracts of interest, commonly known to be affected by MS and including the corticospinal tract, the

anterior thalamic radiation, the parietal branch of the superior longitudinal fasciculus, and the cingulum, were reconstructed by using probabilistic tractography in Tracts Constrained by Underlying Anatomy. The choice of these four tracts was driven by the fact that we needed to select tracts by projecting on distinct and not overlapping cortical areas, preferentially not affected by susceptibility artifacts on 7-T quantitative T2* maps, and that we found to display abnormal quantitative T2* and/or cortical thickness in our MS group relative to control participants.

All individual reconstructed tracts in native diffusion space were realigned on the Montreal Neurological Institute template to allow for group statistics at each voxel along each tract of interest.

For each patient, we obtained mean values of WM and normal-appearing WM fractional anisotropy, axial diffusivity, and radial diffusivity across each section along the realigned tracts, and these values were weighted by the pathway probability at each voxel.

Identification of cortical projection area of WM tract.—

The cortical projection area of each WM tract was identified by using the endpoint map of the tracts of interest provided by Tracts Constrained by Underlying Anatomy, and by projecting the extremity of individual paths on the cortical surface by using FreeSurfer software tools. Because widespread WM degeneration in tracts in MS patients could manifest as more uncertainty in the probabilistic tractography, and hence a more spread out distribution and cortical projection, we defined a cortical projection label for each tract, consistent across patients and control participants. Individual tract cortical projections were normalized on fsaverage, summed across patients and control participants, and given a threshold to create a label of the cortical projection area for each tract common to the entire population (Fig E1). The labels created were used as cortical regions of interest for cortical thickness and T2* measurements on each patient's individual surface.