**Supplemental material 4**

**Magnetic resonance imaging protocol**

**Data acquisition**

MRI for all participants was performed on the same 3T Verio MRI scanner (Siemens Healthcare, Erlangen, Germany) with a 32-channel head coil. Structural imaging data were acquired with T1-weighted (T1W), T2-weighted (T2W), and fluid-attenuated inverse recovery (FLAIR) 3D sequences with 1 mm3 isotropic resolution. Data for diffusion tensor imaging (DTI) were acquired with a twice refocused diffusion-weighted echo-planar imaging (DW-EPI) sequence with 2.3 mm3 resolution and 61 uniform gradient directions with diffusion weighting b = 1000 s/mm2 with 10 interleaved b = 0 measurements. An additional b = 0 dataset with 10 repetitions was subsequently acquired with reversed-phase encoding for correction of artefacts related to susceptibility distortions. Data for magnetisation transfer ratio (MTR) were acquired with a 3D FLASH sequence with 1 mm3 repeated with and without a magnetization transfer preparation (MTon/MToff).1 After the full protocol the T1W sequence was repeated after Gd-administration and a 5 min waiting time for detection of active lesions.

**Structural imaging analysis**

The structural data were co-registered internally and finally registered and resliced to MNI space with the T1W image as reference. T2 white matter lesions regions of interest (ROI) were segmented on FLAIR images by the same person with local thresholding and manual editing supported by the T1W and T2W images using the Jim software (Xinapse systems, UK). New lesions with Gd-enhancement were detected manually. Methods from the FSL software (version 5.0.5, <http://fsl.fmrib.ox.ac.uk/>) package were used for subsequent structural image analysis based on the T1W images.2 Images were at first lesion filled to avoid misclassification of CSF.3 Cross-sectional volumes of the whole brain, cortical grey matter (CGM), and normal-appearing white matter (NAWM) were calculated from probabilistic segmentations produced by SIENAX at a threshold of 50%.4 NAWM was calculated after subtraction of the lesion maps. Longitudinal percentual volume changes were calculated with SIENA. Lesion volume and number of lesions were detected as the volume and number of isolated connected clusters of lesions larger than 6µL in the binary lesion masks. Longitudinal assessment of the number of new or enlarging lesions was done by evaluating volume changes in overlapping regions between the two time points. Lesions not appearing in the first lesion mask were counted as a new lesion, and lesions growing more than 100% in volume from the first to the second scan were counted as enlarging lesions. Thalamus and putamen volumes were segmented with FIRST.5 Spinal cord segmentations producing measures of cross-sectional area (CSA), left-right width (LRW), and anteroposterior width (APW) were performed in the axial plane at the C2/C3-level in the T1W images using a semiautomated method described previously.6 Only CSA is reported.

**Quantitative MRI analysis**

DW-EPI data were pre-processed to correct for subject motion and image distortions from eddy currents and field inhomogeneities using the eddy and top-up tools. 7,8 Mean diffusivity (MD) and fractional anisotropy (FA) were then calculated from DTI estimated with weighted least-squares fitting with dtifit. The MToff images were registered to the MTon images of each participant, and MTR maps were calculated as the percentual reduction in signal due to the MT-pulse as (MToff-MTon)/MToff·100.

Segmented masks of lesions and tissue classes from SIENAX and FIRST were registered and subsampled to the DTI and MTR maps, respectively. Mean values of FA, MD, and MTR from the binary lesion, putamen and thalamus masks were calculated. Estimation of mean FA, MD, and MTR in CGM and NAWM were calculated using a linear mixing model based on the probabilistic segmentations from SIENAX of GM, WM, and CSF.9 Lesions and FIRST segmented deep grey matter were diluted by 2 mm and excluded from this analysis to avoid partial volume effect at their borders.

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