MS Journal Appendix for MRI methodology

Hardware	
Field strength	3.0 Tesla
Manufacturer	Philips
Model	Achieva X-series with Quasar Dual gradients
Coil type (e.g. head, surface)	Combines brain and cervical cord coil
Number of coil channels	12: 8 head, 4 neck

Acquisition sequence		
Type (e.g. FLAIR, DIR, DTI, fMRI)	Brain: MPRAGE, proton density, T2, FLAIR	
Acquisition time	60 minutes	
Orientation	MPRAGE & FLAIR: Sagittal; Proton density & T2: Axial	
Alignment (e.g. anterior commissure/poster commissure line)	Subcallosal line	
Voxel size	MPRAGE and FLAIR: 1 mm³; Proton density and T2: 1 mm²	
TR (msec)	MPRAGE: ~8.19; proton density: ~2000; T2: ~3000; FLAIR: ~8000	
TE	MPRAGE: ~3.75; proton density: ~25; T2: ~80; FLAIR: ~331.6	
TI	MPRAGE/proton density/T2: --- FLAIR: 2,400	
Flip angle	MPRAGE: 8; proton density, T2, and FLAIR: 90	
NEX	MPRAGE, T2, and FLAIR: 1; proton density: 2	
Field of view	MPRAGE & FLAIR: voxels; proton density & T2: in plane resolution	
Matrix size	MPRAGE & FLAIR: 1 mm³; Proton density & T2: 1 mm²	
Parallel imaging	**Yes**	No

Acquisition sequence		
If used, parallel imaging method: (e.g. SENSE, GRAPPA)	FLAIR and MPRAGE: SENSE	
Cardiac gating	Yes	**No**
If used, cardiac gating method: (e.g. PPU or ECG)		
Contrast enhancement	Yes	**No**
If used, provide name of contrast agent, dose and timing of scan post-contrast administration	No contrast was used	
Other parameters:		

Image analysis methods and outputs	
Lesions	
Type (e.g. Gd-enhancing, T2-hyperintense, T1-hypointense)	Enlarged Perivascular Space (ePVS) Score
Analysis method	Visual, ordinal ePVS rating scale on conventional MRI that has been described previously.[1]
Analysis software	NA
Output measure (e.g. count or volume [ml])	ePVS ratings were performed on the basal ganglia, centrum semiovale, and midbrain. Basal ganglia and centrum semiovale PVS were rated 0 (none), 1 (1-10), 2 (11-20), 3 (21-40) and 4 (>40), and midbrain PVS were rated 0 (none visible) or 1 (visible).
Tissue volumes	
Type (e.g. whole brain, grey matter, white matter, spinal cord)	Cerebral T2 Hyperintense Lesion Volume
Analysis method	A processing pipeline created and run within MIPAV's Java Image Science Toolkit (JIST) environment[2] is used to preprocess each subject's MPRAGE and FLAIR scans and run Lesion TOADS. Preprocessing includes MPRAGE brain extraction via SPECTRE (Simple Paradigm for Extra-Cranial Tissue REmoval)[3], co-registration of the series, FLAIR masking, rigid registration of both series to the Montreal Neurological Institute (MNI) 152 T1 1mm brain atlas, and removal of 10 slices from the inferior aspect of each study to reduce field of view. LesionTOADS provides tissue classification and MS lesion segmentation. MIPAV tools are used to overlay a binary lesion mask on to the multichannel MR brain images for manual editing by an experienced MS lesion tracer to correct any false positive designations or omissions. In cases where the segmentation is deemed by the reviewer to have been overestimated by LesionTOADS, default settings are modified with respect to Maximum Grey Matter and Ventricle Distance, LesionTOADS is run again, and the new settings documented for use in follow up scan processing.

Image analysis methods and outputs	
Analysis software	Lesion TOpology-preserving Anatomical Segmentation (LesionTOADS).[4] Lesion TOADS is part of a program plug-in[5] developed for Medical Image Processing And Visualization software (MIPAV).
Output measure (e.g. absolute tissue volume in ml, tissue volume as a fraction of intracranial volume, percentage change in tissue volumes)	Absolute tissue volume in cubic cm
Type (e.g. whole brain, grey matter, white matter, spinal cord)	Whole brain volume
Analysis method	White matter lesions interfere with grey and white matter tissue volume measures and therefore must be addressed prior to processing in cases where the software employed doesn't automatically segment lesion as a separate tissue class. To accomplish this, a copy of the edited T2 Hyperintense Lesion mask is overlaid on the T1 weighted MPRAGE image and edited again by an experienced MS lesion tracer to also include T1 hypointense lesions meeting criteria (T1-hypointense/T2-hyperintense or T2-normal intensity). The edited T1/T2 defined binary mask is then utilized in pre-processing the T1 MPRAGE series. FSL's lesion_filling tool[6] part of FSL[7] uses the mask to fill lesion voxels on the T1 series with intensities similar to neighboring normal appearing tissue voxels to fill in white matter hyperintensities that could otherwise be erroneously labeled as gray matter. T1-weighted MPRAGE images are utilized to determine whole brain volume, normalized for subject head size, using SIENAX,[8] part of FSL.[7] SIENAX is run with options selected for improved removal of non-brain tissue and also to provide separate estimated volumes of grey matter, white matter, peripheral grey matter, and ventricular CSF.[9]
Analysis software	SIENAX,[8] part of FSL[7]

Image analysis methods and outputs	
Output measure (e.g. absolute tissue volume in ml, tissue volume as a fraction of intracranial volume, percentage change in tissue volumes)	Absolute tissue volume in cubic cm
Type (e.g. whole brain, grey matter, white matter, spinal cord)	Cortical thickness

Image analysis methods and outputs	
Analysis method	This processing includes removal of non-brain tissue using a hybrid watershed/surface deformation procedure,[10] automated Talairach transformation, tessellation of the gray matter white matter boundary, automated topology correction,[11, 12] and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class.[13-15] Once the cortical models are complete, a number of deformable procedures can be performed for in further data processing and analysis including surface inflation, registration to a spherical atlas which utilized individual cortical folding patterns to match cortical geometry across subjects,[13] parcellation of the cerebral cortex into units based on gyral and sulcal structure,[16, 17] and creation of a variety of surface based data including maps of curvature and sulcal depth. This method uses both intensity and continuity information from the entire three dimensional MR volume in segmentation and deformation procedures to produce representations of cortical thickness, calculated as the closest distance from the gray/white boundary to the gray/CSF boundary at each vertex on the tessellated surface.[15] The maps are created using spatial intensity gradients across tissue classes and are therefore not simply reliant on absolute signal intensity. The maps produced are not restricted to the voxel resolution of the original data thus are capable of detecting submillimeter differences between groups. Procedures for the measurement of cortical thickness have been validated against histological analysis[18] and manual measurements.[19, 20] Freesurfer morphometric procedures have been demonstrated to show good test-retest reliability across scanner manufacturers and across field strengths.[21, 22]
Analysis software	Freesurfer image analysis suite, which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/).

Image analysis methods and outputs	
Output measure (e.g. absolute tissue volume in ml, tissue volume as a fraction of intracranial volume, percentage change in tissue volumes)	Tissue thickness in mm
Tissue measures (e.g. MTR, DTI, T1-RT, T2-RT, T2*, T2', ¹H-MRS, perfusion, Na)	
Type (e.g. whole brain, grey matter, white matter, spinal cord, normal-appearing grey matter or white matter)	NA
Analysis method	NA
Analysis software	NA
Output measure	NA
Other MRI measures (e.g. functional MRI)	
Type (e.g. whole brain, grey matter, white matter, spinal cord, normal-appearing grey matter or white matter)	NA
Analysis method	NA
Analysis software	NA
Output measure	NA

Other analysis details:

References:

1. Potter GM, Chappell FM, Morris Z, et al. Cerebral perivascular spaces visible on magnetic resonance imaging: development of a qualitative rating scale and its observer reliability. *Cerebrovasc Dis* 2015; 39: 224-231. 2015/04/01. DOI: 10.1159/000375153.
2. Lucas BC, Bogovic JA, Carass A, et al. The Java Image Science Toolkit (JIST) for rapid prototyping and publishing of neuroimaging software. *Neuroinformatics* 2010; 8: 5-17. 2010/01/16. DOI: 10.1007/s12021-009-9061-2.
3. Carass A, Cuzzocreo J, Wheeler MB, et al. Simple paradigm for extra-cerebral tissue removal: algorithm and analysis. *Neuroimage* 2011; 56: 1982-1992. 2011/04/05. DOI: 10.1016/j.neuroimage.2011.03.045.
4. Shiee N, Bazin PL, Ozturk A, et al. A topology-preserving approach to the segmentation of brain images with multiple sclerosis lesions. *Neuroimage* 2010; 49: 1524-1535. 2009/09/22. DOI: 10.1016/j.neuroimage.2009.09.005.
5. Bazin PL and Pham DL. Homeomorphic brain image segmentation with topological and statistical atlases. *Med Image Anal* 2008; 12: 616-625. 2008/07/22. DOI: 10.1016/j.media.2008.06.008.
6. Battaglini M, Jenkinson M and De Stefano N. Evaluating and reducing the impact of white matter lesions on brain volume measurements. *Hum Brain Mapp* 2012; 33: 2062-2071. 2011/09/02. DOI: 10.1002/hbm.21344.

7.   Smith SM, Jenkinson M, Woolrich MW, et al. Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage* 2004; 23 Suppl 1: S208-219. 2004/10/27. DOI: 10.1016/j.neuroimage.2004.07.051.

8.   Smith SM, Zhang Y, Jenkinson M, et al. Accurate, robust, and automated longitudinal and cross-sectional brain change analysis. *Neuroimage* 2002; 17: 479-489. 2002/12/17. DOI: 10.1006/nimg.2002.1040.

9.   Zhang Y, Brady M and Smith S. Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. *IEEE Trans Med Imaging* 2001; 20: 45-57. 2001/04/11. DOI: 10.1109/42.906424.

10.   Segonne F, Dale AM, Busa E, et al. A hybrid approach to the skull stripping problem in MRI. *Neuroimage* 2004; 22: 1060-1075. 2004/06/29. DOI: 10.1016/j.neuroimage.2004.03.032.

11.   Fischl B, Liu A and Dale AM. Automated manifold surgery: constructing geometrically accurate and topologically correct models of the human cerebral cortex. *IEEE Trans Med Imaging* 2001; 20: 70-80. 2001/04/11. DOI: 10.1109/42.906426.

12.   Segonne F, Pacheco J and Fischl B. Geometrically accurate topology-correction of cortical surfaces using nonseparating loops. *IEEE Trans Med Imaging* 2007; 26: 518-529. 2007/04/13. DOI: 10.1109/TMI.2006.887364.

13.   Dale AM, Fischl B and Sereno MI. Cortical surface-based analysis. I. Segmentation and surface reconstruction. *Neuroimage* 1999; 9: 179-194. 1999/02/05. DOI: 10.1006/nimg.1998.0395.

14.   Dale AM and Sereno MI. Improved Localizadon of Cortical Activity by Combining EEG and MEG with MRI Cortical Surface Reconstruction: A Linear Approach. *J Cogn Neurosci* 1993; 5: 162-176. 1993/04/01. DOI: 10.1162/jocn.1993.5.2.162.

15.   Fischl B and Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc Natl Acad Sci U S A* 2000; 97: 11050-11055. 2000/09/14. DOI: 10.1073/pnas.200033797.

16.   Desikan RS, Segonne F, Fischl B, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage* 2006; 31: 968-980. 2006/03/15. DOI: 10.1016/j.neuroimage.2006.01.021.

17.   Fischl B, van der Kouwe A, Destrieux C, et al. Automatically parcellating the human cerebral cortex. *Cereb Cortex* 2004; 14: 11-22. 2003/12/05. DOI: 10.1093/cercor/bhg087.

18.   Rosas HD, Liu AK, Hersch S, et al. Regional and progressive thinning of the cortical ribbon in Huntington's disease. *Neurology* 2002; 58: 695-701. 2002/03/13. DOI: 10.1212/wnl.58.5.695.

19.   Kuperberg GR, Broome MR, McGuire PK, et al. Regionally localized thinning of the cerebral cortex in schizophrenia. *Arch Gen Psychiatry* 2003; 60: 878-888. 2003/09/10. DOI: 10.1001/archpsyc.60.9.878.

20.   Salat DH, Buckner RL, Snyder AZ, et al. Thinning of the cerebral cortex in aging. *Cereb Cortex* 2004; 14: 721-730. 2004/04/01. DOI: 10.1093/cercor/bhh032.

21.   Han X, Jovicich J, Salat D, et al. Reliability of MRI-derived measurements of human cerebral cortical thickness: the effects of field strength, scanner upgrade and manufacturer. *Neuroimage* 2006; 32: 180-194. 2006/05/03. DOI: 10.1016/j.neuroimage.2006.02.051.

22.   Reuter M and Fischl B. Avoiding asymmetry-induced bias in longitudinal image processing. *Neuroimage* 2011; 57: 19-21. 2011/03/08. DOI: 10.1016/j.neuroimage.2011.02.076.