Glutamate Sensitive Imaging and Evaluation of Cognitive Impairment in Multiple Sclerosis

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Supplementary Methods

MRI acquisition parameters

A 3D Magnetization Prepared Rapid Acquisition Gradient Recalled Echo (MPRAGE) anatomical image with a field of view covering the whole brain was obtained for segmentation (3D Turbo Field Echo (TFE), factor=256, TR/TE/flip angle=2.8ms/1.3ms/7°, inversion delay=1300 ms, SENSE=2, field of view (FOV)=256x256x172.5 mm^3, 1.25 mm^3 isotropic resolution reconstructed to 1.1 mm^3).

The center of the CEST slice was placed approximately 20 mm above the anterior commissure - posterior commissure (AC-PC) line. The CEST sequence consisted of a 2D multi-shot TFE sequence (factor=3, TR/TE/flip angle=5.6ms/2.7ms/10°, FOV=240x240 mm^2, 1.87x1.87x10 mm^3 resolution). The CEST saturation pulse (4.25 μT pulse train of 10 ms Gaussian pulses, 90% duty cycle, 100 ms total duration) was performed at 49 equally-spaced offset frequencies swept between $\Delta\omega$=+/-5.0 ppm and one reference (S_0, $\Delta\omega$=80.0 ppm). The total CEST scan time was 11:37 minutes. An additional T_1-weighted anatomical volume was obtained with the same geometry as

the CEST slice in order to facilitate registration of the CEST slice with segmented tissue masks derived from the MPRAGE volume.

A B_1 map for the CEST slice was obtained in the same geometry and resolution using the double angle method.[1, 2] The sequence consisted of a 2D multi-shot Turbo Spin Echo (TSE) readout sequence (factor=15, TR/TE=6000ms/12ms) acquired at two flip angles (60° and 30°).

Image processing: B_1 and B_0 correction of CEST data

CEST z-spectra were corrected voxel-wise for B_1 inhomogeneity using a B_1 percentage map computed using the double angle method.[1, 2] The effective local flip angle ($\alpha_{effective}$) was determined from the signal ratio for images acquired at flip angles α and 2α (α=30°), and the percentage of the desired B_1 field (computed as $\alpha_{effective}/\alpha$ x 100 for each voxel) was used to scale the z-spectra. Z-spectra were corrected for B_0 inhomogeneity by centering each voxel's z-spectrum to $\Delta\omega$=0 using a symmetry-based algorithm. The B_0 correction method consisted of mirroring the z-spectrum about $\Delta\omega$=0, then determining the frequency shift that, when applied to the mirrored spectrum, minimizes the mean squared error between the mirrored spectrum and the original spectrum. This procedure assumes the z-spectra are approximately symmetric near $\Delta\omega$=0. The B_0 frequency shift was calculated on a voxel-by-voxel basis, and the resulting shift map was used to center the CEST z-spectrum for each voxel. All shifted, centered z-spectra were interpolated to the original frequency offsets acquired.

Segmentation

Tissue masks for GM, WM, and CSF were segmented in SPM12 from the MPRAGE using the "Segment" tool. Default settings were modified to improve performance on the 7T MPRAGE volumes (bias regularization = "extremely light", bias FWHM = "30 mm cutoff", and clean up procedure = "thorough"). GM was further divided into distinct cortical regions using a multi-atlas labeling procedure applied to the MPRAGE volume.[3] The MPRAGE volume and segmented tissue masks were then co-registered to the anatomical volume obtained with the CEST geometry using the "Coregister: Estimate and Re-slice" tool and "Normalized Mutual Information" function in SPM12. Finally, the tissue masks were registered to the non-saturated CEST acquisition (S_0) using FLIRT linear registration (normalized mutual information function) in FSL.[4] In order to minimize partial volume effects from CSF, voxels in the initial cortical GM mask with a CEST z-spectrum full-width-at-half-max (FWHM) value less than 95% of the average GM FWHM were excluded, as a narrow peak at $\Delta\omega$=0 ppm is characteristic of CSF.

Supplementary References

1. Insko EK and Bolinger L. Mapping of the Radiofrequency Field. *Journal of Magnetic Resonance, Series A* 1993; 103: 82-85. DOI: http://dx.doi.org/10.1006/jmra.1993.1133.

2. Stollberger R and Wach P. Imaging of the active B1 field in vivo. *Magn Reson Med* 1996; 35: 246-251.

3. Asman AJ and Landman BA. Hierarchical performance estimation in the statistical label fusion framework. *Medical image analysis* 2014; 18: 1070-1081. DOI: 10.1016/j.media.2014.06.005.

4. Jenkinson M and Smith S. A global optimisation method for robust affine registration of brain images. *Medical image analysis* 2001; 5: 143-156.