Quantifying MRI with increased specificity for MS pathology: A longitudinal method for obtaining whole-brain metrics of 3D maps derived from non-conventional MRI

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Abstract: Three-dimensional maps derived from non-conventional MRI have increased specificity for MS pathology, and whole-brain metrics based on these maps could clarify the evolution of pathology occurring concurrently with atrophy and affecting the remaining brain tissue. However, cross-sectional analysis to calculate longitudinal change is suboptimal as it may be affected by inconsistent voxel populations being analyzed due to atrophy occurring between scans. We developed a longitudinal method, including non-brain-constrained-symmetric registration and joint-brain-mask calculation, to ensure evaluation of the whole-brain metric on the same voxels at both timepoints. We demonstrate that the approach is necessary and sufficiently accurate for use in clinical trials of MS therapies.

Introduction: Although focal inflammatory demyelinated white-matter (WM) lesions are characteristic of multiple sclerosis (MS), post-mortem histopathology of the brains of MS patients has also revealed a substantial burden of disease in extra-lesional WM and in grey-matter (GM). Thus, whole-brain-based MR metrics may have advantages over metrics based only on lesions. Three-dimensional maps derived from non-conventional imaging have shown increased specificity to different types of MS pathology, and whole-brain metrics based on these 3D maps could clarify the evolution MS pathology that occurs concurrently with brain volume change.
The assessment of change over time based on repeated cross-sectional metrics is suboptimal due to several factors. In the case of patients who undergo significant brain atrophy over time, earlier timepoints will include brain tissue that no longer exists at later timepoints. In this case, due to spatial heterogeneity within the brain, the whole-brain metric may exhibit misleading "improvement" over time, due to the loss of brain tissue with the most pathological values.

To minimize this, we developed a longitudinal methodology for obtaining whole-brain metrics of 3D maps derived from non-conventional imaging based on: i) linear "non-brain"-constrained symmetric registration to align brain images obtained from the same subject at different timepoints, thus minimizing the variability due to rescanning (e.g. changes of head angulation, changes of head position relative to the head coil, changes in temperature), and ii) calculation of joint-brain-masks to ensure that the whole-brain metric is evaluated on the same brain voxels at both timepoints.

Methods: Registration and calculation of the joint-brain-masks was performed on axially acquired T1w MRI, 1mm^2 in-plane resolution, 3mm slice thickness, with no gaps. *Linear "non-brain"-constrained symmetric registration.* The multi-step hierarchical registration strategy uses the head, brain, and non-brain as targets (Fig. 1), and is similar to SIENA's skull-constrained registration (Smith et al., 2002). In each step of the non-brain-constrained algorithm, the intermediate transformation matrix is calculated using an intensity-based registration maximizing the cross-correlation of source and target images (minctracc, Collins et al., 1994). The strategy begins with *R1*, an initial rigid-body whole head registration, mapping baseline data to a subsequent time point. All subsequent transformations are full affine, to accommodate simple image distortions. *R1* is then used as the initial conditions to estimate *R2*, a registration of brain to brain. *R2* is used as input to compute *R3*, a registration of a cropped "non-brain" region of the source MRI to a cropped "non-brain" region of the target MRI (cropping minimizes the effects of artifacts often present at the top of the head, and the variable appearance of neck fat related to neck flexion-extension). *R3* is used as the initial conditions to compute *R4*, a 6-parameter affine registration of brain-to-brain, optimizing translations and rotations while keeping scales and skews fixed. This procedure results in a "non-brain-constrained" linear registration. To achieve a symmetric solution, non-brain constrained linear transformation matrices are calculated for both the forward and backward registrations, followed by averaging the forward transformation with the inverse of the backward, resulting in *R5*. *Calculation of joint-brain-masks.* GM and WM probability maps are calculated independently for each timepoint using a probabilistic tissue classification (FAST, FSL, Zhang et al., 2001). To minimize partial-volume effects, binary high-tissue-probability masks are created by thresholding the GM and WM probability maps at 75% and combining them. These masks are then transformed using *R5*, followed by an intersection operation of the co-registered masks to yield a 3D binary mask of the common brain tissue voxels, present at both timepoints. This mask is then transformed to each timepoint's native-space. Using this 3D binary joint-brain-mask, the whole-brain metric can be evaluated on the same brain regions at both timepoints. (See Fig. 2 for illustration of this procedure on MTR maps.)

Figure 1

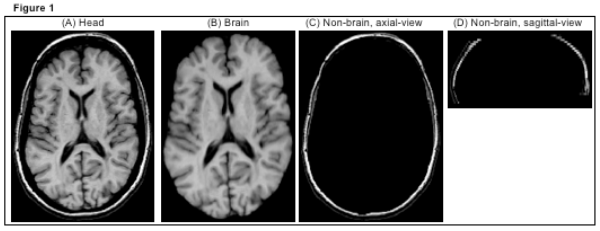
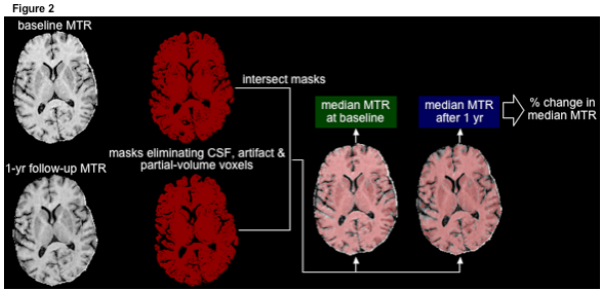


Figure 2



Validation. We validated the necessity of the longitudinal methodology by demonstrating that atrophy (i.e. a loss of some brain voxels) may significantly change whole-brain metric values even if there is no change in MTR and T2 relaxation times in the remaining voxels. The baseline and 1-year data from 8 MS patients were analyzed. This group exhibited a median loss of brain volume of 2.6 % (IQR=1.6, 3.7 %) over a median of 17 mo (IQR=17, 22 mo). To determine the effect of this loss of volume on the whole-brain metrics in the absence of any change in the underlying 3D maps of MTR and T2 relaxation time, the median MTR and the mode of the T2 relaxation time distribution were calculated on the baseline scans within 2 different populations of voxels: 1) a population of voxels with high "baseline tissue-specific probability", identified on the baseline scan; 2) a sub-population of "atrophy-unaffected" voxels with high tissue-specific probability, identified on the joint-brain-mask. *Assessment of accuracy.* We assessed the error in accuracy of the change in whole-brain metrics by calculating the percentage change in the median of the MTR values and the mode of the distribution of T2 relaxation times in the whole-brain on scan-reposition-rescan data. MTR data was available in 3 MS patients. MTR and T2 relaxation data were available for 4 healthy control subjects.

Results: *Validation.* The median MTR at baseline was consistently higher in all subjects (mean increase=1.3 %, SD=0.31 %, $p<0.001$, T-test) and the median absolute percentage change in the mode of the T2 relaxation time distribution was also significantly higher (median absolute increase=0.31 %, IQR=0.01, 1.58 %, $p=0.03$, Wilcoxon signed rank) when calculated based on the "atrophy-unaffected" sub-population of voxels relative to the larger "baseline high tissue-specific probability" voxel population, indicating that misleading significant results can be obtained purely due to small changes in the voxel populations assessed, and validating the necessity of using joint-brain-masks. *Assessment of accuracy.* The mean and median percentage change between the same-day scans were not significantly different from 0 (T-test and Wilcoxon signed rank test) indicating that the method is not biased. The median absolute error in the calculation of change in whole-brain median MTR was 0.3 %, and for change in the mode of the T2 relaxation time it was 1.4%.

Conclusions: We have shown that cross-sectional calculation of longitudinal changes in whole-brain MTR and T2 relaxation are significantly affected by inconsistent voxel populations analyzed at baseline and follow-up due to brain atrophy. To address this problem, we developed a longitudinal method that includes a linear "non-brain"-constrained symmetric registration, and the calculation of joint-brain-masks to ensure that the whole-brain metric is evaluated on the same brain voxels at both timepoints. The accuracy of the method for measuring change in whole-brain MTR and T2 relaxation is likely to be adequate for detecting therapy-related changes that may occur.

Acknowledgements: The Canadian MS/BMT trial is funded by the Multiple Sclerosis Scientific Research Foundation