Quantitative Volumetrics of Multiple Sclerosis Brain from 7T MRI

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Introduction: There are important advantages of conducting in vivo MRI studies at ultra-high magnetic field including improved signal to noise, increased spatial resolution, and novel contrast; properties that could substantially improve our ability to visualize disease pathology. However, ultra-high field MRI advantages often are accompanied by technical challenges, such as increased SAR, and $\mathbf{B_0}$ and $\mathbf{B_1}$ inhomogeneities . Here we describe an iterative approach to signal intensity bias correction, brain extraction and segmentation of MRI acquired at 7T that was used to investigate brain volume changes in patients with Multiple Sclerosis (MS).

Methods: Healthy control subjects (n=13, mean age: 49±9; range 24-65 years, 7 women and 5 men) and subjects with multiple sclerosis (n=18, mean age: 48±10; range 28-62 years, 11 women, 7 men) were recruited and enrolled in an Institutional Review Board approved protocol. Subjects with MS went through a self-reported Expanded Disability Status Score (EDSS) assessment test (scores range = 2.0-6.5, median = 4.0). Mean disease duration was 12.6 years (range 3-25 years). MR data acquisitions were performed on a whole-body 7T Siemens MAGNETOM system using an eight-channel phased-array ^{1}H RF coil (Rapid Biomedical). After $\mathbf{B_0}$ shimming and RF pulse calibration, high resolution 3D data sets with MPRAGE (TR = 2.3 s, TI = 1.05 s, flip angle = 6^0, isotropic resolution of 0.8 mm, TA = 10.8 min) were acquired. In addition, four sets of whole brain MRI data were acquired at inversion times (TI) of 300, 900 and 2000 ms; and without inversion pulse (FOV: 192 mm x 256 mm x 192 mm, matrix: 192 x 256 x 96, TR = 2.5 s, TE = 2.3 ms, TA = 4.5 min) to calculate, R_1 maps by solving the Bloch equation. Fluid Attenuated Inversion Recovery (FLAIR) sequences (TR=8 s, isotropic spatial resolution of 0.8 mm, TI = 2.15 s, matrix: 280 x 320 x 208, TA = 9.6 min) also were acquired.

An initial estimation of the RF bias field was obtained using a 3D Gaussian smoothing kernel (sigma 10 mm). This smoothing step creates an image that approximates the low spatial frequency variance due to B_1 inhomogeneity. The original image was then divided by this smoothed image and normalized by the mean intensity of the original image. This same smoothing step was also applied to a binary mask image, which is used to limit the bias estimation and correction to areas within the mask. The bias corrected image was then linearly registered to a standard space template (Montreal Neurological Institute (MNI152_T1_2mm)) and a dilated standard space brain mask was transformed into native space [1, 2]. Voxels representing areas outside of the brain were then identified on the native space bias corrected image [3] and these results were edited with the transformed dilated standard space brain mask. These registration and editing steps were repeated to obtain the final brain mask and an estimation of skull size [3]. The original image was then masked with this final brain mask and bias estimation and correction were applied to this image as described above. Bright voxels were lowered to the intensity of the brightest 98th percentile of the original image. Tissue segmentation into gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) was carried out using FMRIB's Automated Segmentation Tool (FAST) using standard space tissue prior probability estimates to initialize the process[4]. This segmentation step also provides additional estimation and correction of the bias field using each of the three tissue classes as references [4]. Subcortical GM structure segmentation was improved using FMRIB's Integrated Registration and Segmentation Tool (FIRST), which uses shape and intensity based models to segment subcortical brain structures [5]. WM definition was improved by registering the R_1 map using affine linear registration [1,2] and a setting lower bounds limit for WM R_1 values of 0.5 s^{-1}. White matter lesions were identified using a semi-automated technique that combined the gray matter segmentation results along with atlas based probability maps of white matter distribution. This combination identified voxel clusters that had hypointense values within the spatial distribution of white matter. These clusters were then manually edited and compared to hyperintensities on the co-registered FLAIR image in order to obtain final white matter lesion volumes. Tissue volumes were normalized using a scaling factor based on skull size [6]. All processing steps, except lesion identification, were fully automated. Summary pages containing representative images from each subject for each of these steps were generated and inspected for quality. Group differences in normalized brain volumes were analyzed with analysis of covariance adjusting for age.

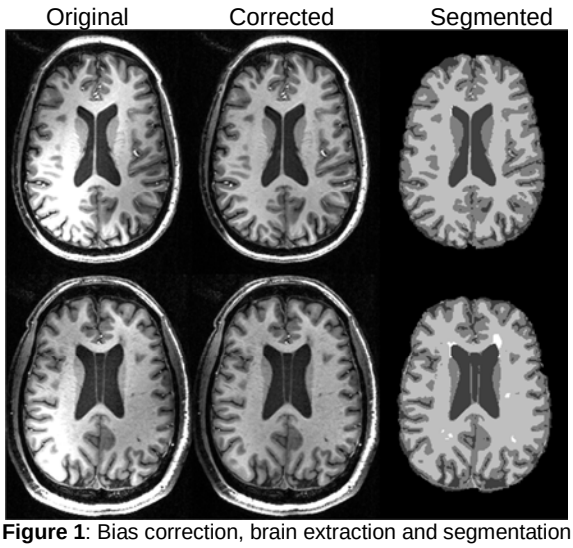

Figure 1: Bias correction, brain extraction and segmentation in a control subject (top) and a subject with MS (bottom).

Results and Discussion: The post processing steps resulted in significant improvements to the RF bias and allowed for robust and accurate brain identification and segmentation in all subjects (**Figure 1**). Increasing age was associated with lower normalized gray matter volumes (R^2=0.54, p<0.0001), and increased CSF volumes (R^2=0.12, p=0.034). As expected, the volumes of hypointense regions in the white matter were greater in subjects with MS (F(1,28=8.46, p=0.007). Although MS subjects had nominally lower gray matter and white volumes (**Table 1**), we were unable to detect any significant group differences in these measurements. This preliminary study demonstrates the feasibility and effectiveness of an iterative and integrative approach that can be used for volumetric analysis of 7T images from controls and MS subjects.

	Control	**MS**
Gray Matter (cm^3)	849±74	843±65
White Matter (cm^3)	759±65	730±75
Cerebrospinal Fluid (cm^3)	469±45	480±42
White Matter Lesion (cm^3)	0.98±1.8	3.6±3.0

Table 1: Brain tissue volumes in MS subjects and controls.

1. Jenkinson, M. & Smith, S. Med Image Anal 2001; 5(2): 143-15; **2.** Jenkinson M, Bannister P, Brady, Michael & Smith, Stephen. Neuroimage 2002; 17(2): 825-841; **3.** S.M. Smith. Human Brain Mapping, 17(3):143-155; **4.** Zhang, Y., Brady, M. & Smith, S. IEEE Trans Med Imaging 2001; 20(1): 45-57; **5.** Patenaude, B., Smith, S.M., Kennedy, D., and Jenkinson M. NeuroImage, 56(3):907-922, 2011; **6.** Smith, S. M., Zhang, Y., Jenkinson, M., Chen, J., Matthews, P. M., Federico, A. & Stefano, N. D. Neuroimage 2002; 17:479-489.