Atlas-Based Segmentation of Quantitative Susceptibility Maps: Determining Iron Content in Deep Gray Matter Structures

Issel Anne L. Lim[1,2], Andreia V. Faria[1], Xu Li[1,2], Johnny T.C. Hsu[1], Raag D. Airan[1], Susumu Mori[1,2], and Peter C.M. van Zijl[1,2]

[1]*Radiology, Johns Hopkins University, Baltimore, Maryland, United States,* [2]*F.M. Kirby Research Center for Functional Brain Imaging, Kennedy Krieger Institute, Baltimore, Maryland, United States*

Target Audience: Researchers and clinicians interested in the brain, especially iron content and susceptibility mapping.

Purpose: Brain iron concentration has been reported to change in several neurodegenerative disorders. Quantitative Susceptibility Mapping (QSM) methods have shown correlations between magnetic susceptibility and iron content in brain gray matter (GM).[1-4] Currently, the average susceptibility for a brain structure is determined through manual delineation. For large data sets (group studies), analysis would be time-consuming and limited by human error. An alternative approach uses stereotaxic atlases as a frame of reference; automated coregistration between subject and atlas allows for efficient segmentation of the subject brain. For example, the Eve atlas from Johns Hopkins University is a single-subject human brain with 1mm^3 isotropic resolution in standard Montreal Neurological Institute (MNI) coordinates.[5] Regions of interest (ROIs) in the DTI-based White Matter Parcellation Map (WMPM, Fig. 1a) in this atlas are based on white matter orientation and tract structures. However, when overlaid on QSM images (Fig. 1b), these ROIs do not align perfectly with GM structures, which have very low fractional anisotropy. After defining GM regions on QSM maps to create a new deep GM parcellation map (DGMPM) and combining these ROIs with the WMPM, we created the "EvePM," or "Everything" Parcellation Map (Fig. 1c), allowing automated segmentation of QSM images for over sixty brain regions in less than 24 hours for five subjects. The average susceptibility for GM regions can then be correlated with brain iron concentration if a calibration curve is available, for which literature values from age-dependent postmortem studies were used.[6]

Methods: Five healthy male subjects (aged 30-33) were studied after IRB approval and written informed consent on a 3T Philips system (dual-channel body-coil excitation, 32-channel head receive). Subjects were scanned at four orientations with respect to the B_0 field.[1,3,7] Phase images were acquired with a 3D ten-echo GRE sequence (SENSE=2x1x2, TR=70ms, TE_1=6ms, ΔTE=6ms, α=20°, fat suppressed, 9:19min). An MPRAGE was also acquired (3D GRE turbo-field echo readout factor=184, shot interval=3500ms, SENSE=1x1x2, TI/TE/TR=1000/3.2/7.0ms, α=8°). MPRAGE and GRE covered the entire brain (acquired resolution=1.2mm isotropic). Using MATLAB, susceptibility maps were calculated using COSMOS,[1,7] with Laplacian-based phase unwrapping.[2] The Eve atlas contains a T_1-weighted MPRAGE from a single subject. We scanned this subject, then used AIR[8,9] to coregister our acquired MPRAGE to the atlas MPRAGE. We applied the transformation matrices to the subject's GRE 4th-echo magnitude image (GreMag) and QSM, adding them as atlas templates in MNI coordinates. The WMPM and DGMPM were combined to create the EvePM. The outer surface of each male GreMag was coregistered to the Eve atlas GreMag with AIR, and the internal structures for each subject were coregistered with dual-channel Large Deformation Diffeomorphic Metric Mapping (LDDMM)[10,11] using both the GreMag and QSM. The resulting transformation matrices were inverted and applied to the EvePM, transforming over sixty ROIs into subject space. The average susceptibility was referenced using a grouped deep WM structure ROI set to -0.03ppm, corresponding to an average of 0ppm in CSF. As a consequence, brighter contrast in the QSM indicates structures more paramagnetic than CSF[7]. Accuracy of the segmentation methods was assessed using a kappa analysis[12]; each subject brain was coregistered to the Eve atlas with AIR, then three human raters drew the left and right structures of six ROIs across the same four to eight axial slices, which were compared to automated segmentation with the EvePM to measure inter-rater reliability. To assess intra-rater reliability, one human rater drew the ROIs at two separate times, with the second time designated as the gold standard. Brain iron concentrations determined as a function of age in the globus pallidus (GP), putamen (PT), and caudate nucleus (CN) from Hallgren and Sourander[6] were used to linearly calibrate susceptibility versus iron, from which the brain iron concentration for other deep GM regions could be determined (Fig. 2b).

Results: Figure 1 shows the axial, sagittal, and coronal planes of the parcellation maps. The kappa statistic was 0.85 between automated and manual segmentation, 0.89 between human raters, and 0.94 for intra-rater reliability, suggesting "almost perfect" agreement (kappa = 0.81 to 1.0) between all methods. Figure 2a shows the magnetic susceptibility for nine deep GM structures in our five 30- to 33-year-old volunteers, which was linearly correlated for the GP, PT, and CN with age-based iron concentration from[6] (Fig. 2b, R^2 = 0.997). The average susceptibility for other GM ROIs was plotted along this line (Fig. 2b), providing an estimate of their average brain iron concentration (Fig. 2c).

Discussion: The increase in contrast and spatial resolution provided by QSM versus DTI improved the definition of deep GM ROIs in the Eve atlas, allowing automated reproducible quantification of magnetic susceptibility. We found our automated segmentation to have comparable accuracy to manual multiple-rater delineation and to be more efficient; manual delineation of twelve ROIs across five subjects took three weeks, whereas automated delineation of >60 ROIs took less than 24 hours. Brain iron concentration is not straightforward to determine, as it changes with age. Future work involves measuring baseline susceptibility at different ages to determine brain iron concentration throughout development and aging.

Conclusion: This atlas provides a automated and time-efficient tool for coregistering and segmenting many regions of interest for quantitative susceptibility data, thereby allowing the correlation of susceptibility measurements with brain iron concentration, which has been suggested to be a potential noninvasive biomarker of neurodegeneration or aging. Images exhibiting different types of contrast that have been coregistered to the atlas can also be segmented in an automated fashion, allowing for direct comparison of quantitative metrics between different modalities.

Funding: NIH-P41 EB051909, NIH 5 T32 MH015330.

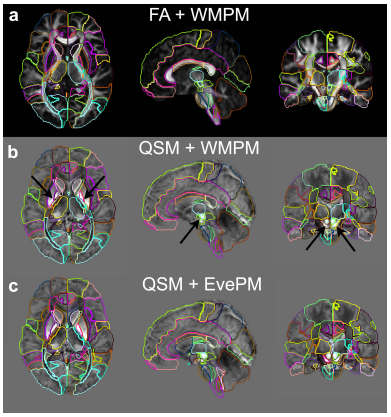

Figure 1: (a) WMPM on FA map in Eve Atlas. (b) Misaligned ROIs from WMPM on QSM. (c) Resolved ROIs in EvePM.

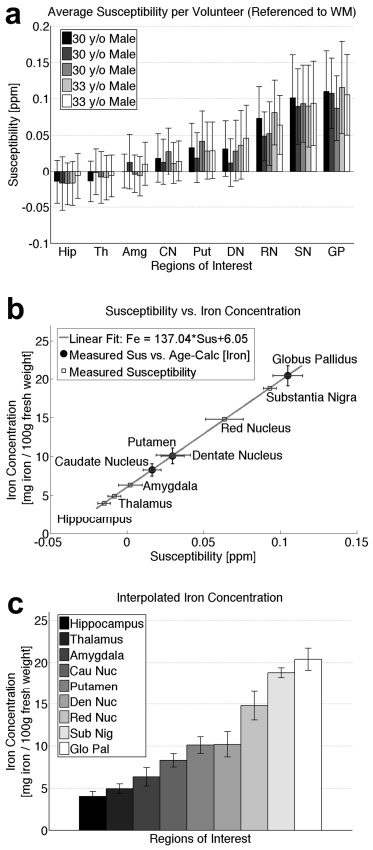

Figure 2: (a) Average susceptibility in GM. (b) Linear correlation: susceptibility and [iron]. (c) Estimated [iron].

References: 1) Liu T, et al. MRM 2009;61:196-204. 2) Li W, et al. NeuroImage 2011;55:1645-56. 3) Wharton S & Bowtell R. NeuroImage 2010;53:515-25. 4) Schweser F, et al. NeuroImage 2011;54:2789-807. 5) Mori S, et al. Brain 2008;40:570-82. 6) Hallgren B & Sourander P. JNeurochem 1958;3:41-51. 7) Li X, et al. NeuroImage 2012;62:314-30. 8) Woods RP, et al. JCAT 1998;22:139-52. 9) Woods RP, et al. JCAT 1998;22:153-65. 10) Beg MF, et al. IJCV 2005;61:139-57. 11) Cao Y, et al. IEEE Trans Med Imaging 2005;24:1216-30. 12) Landis JR & Koch GG. Biometrics 1977;33(159-74).