Quantification of Susceptibility Mapping with Synchrotron X-ray Fluorescence Iron Mapping

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Introduction. Susceptibility weighted imaging (SWI) has been widely accepted as an *in vivo* neuroimaging technique for monitoring neurologic disorders with iron-related susceptibility changes [1]. Susceptibility mapping (SWIM) yields a quantitative susceptibility map calculated from SWI phase information and can be used to predict iron content *in vivo*. The most important aspect of susceptibility mapping is that it is not sensitive to the relative orientation of a structure with respect to the main field. Wharton and Bowtell [2] have estimated the relationship between average susceptibility of some major brain structures and their non-heme iron content based on the work of Hallgren and Sourander [3]. Here for the first time, the quantitative elemental mapping technique, synchrotron Rapid Scanning X-ray Fluorescence (RS-XRF) [4], was used to determine the relationship between susceptibility and iron concentration, on a voxel by voxel basis in the same brain structures.

Methods. Two formalin fixed coronal sections of human cadaveric multiple sclerosis (MS) brains (three hemispheres) were obtained from the Human Brain and Spinal Fluid Resource Center (HSB), Los Angeles, CA under university ethics approval. The clinical diagnoses were confirmed by post-mortem pathology. Hemispheres were embedded in gelatin for MRI and then sectioned for XRF scans.

MR Images were collected on a 3T Siemens Verio system using a T2* weighted multi-echo SWI sequence with 11 echoes (TR=40ms, FA=15°) . The images were acquired with resolution 0.5mmx0.5mm in phase and readout directions and 0.7mm in slice direction (coronal) with a bandwidth of 465Hz/pixel, a field-of-view of 256mm x 192mm resulting in 512 x 384 matrix for 40 slices. The shortest echo time was 5.68ms with a 2.57ms increment for the other 10 echoes. MR phase images were first filtered by a 64x64 high pass filter and then processed using the SWIM algorithm [5] to create susceptibility maps using software SPIN (Signal Processing in NMR, Detroit, MI, USA).

After MR imaging, the region of interest was identified in MR images; and the brain hemispheres were sectioned for synchrotron imaging. RS-XRF images were acquired at wiggler beam line 10-2 at the Stanford Synchrotron Radiation Lightsource (SSRL). The samples were mounted on a set of motorized stages oriented at 45° to the incident beam. The incident beam (12 keV) passing through a tantalum aperture produced a 100 μm x 100 μm spot on the sample which was raster-scanned in the beam using a dwell time of 15ms/point. Fluorescent energy windows were centered for Fe (6.21 - 6.70 keV) as well as all other biologically interesting elements, scatter and total incoming counts. The data were quantified in μg Fe/g w/w tissue using Sam's Microanalysis kit (http://ssrl.slac.stanford.edu/~swebb/smak.html) as previously described (6)

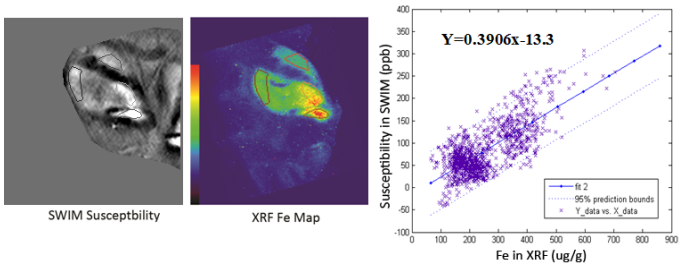

Fig.1. Registration of SWIM susceptibility map (TE=8.25ms) and XRF Fe map and their correlation

A registration pipeline was developed in MATLAB code to register the 2D XRF data into 3D MRI data volume. An iterative closest point (ICP) algorithm was first used to insert the 2D XRF features into the 3D MR features to find the best location and orientation of sectioning; then a 2D non-rigid registration was applied to get the best match of features voxel by voxel considering possible deformation of brain tissues.

Results. The 2D XRF Fe maps of 3 MS hemispheres were registered with their corresponding SWIM susceptibility maps. Fig. 1 is an example of the registration performance and the fitting between XRF iron concentration and SWIM susceptibility in the putamen and caudate. In our results, 1μg Fe/g tissue corresponds to 0.39~0.41ppb susceptibility change with respect to the surrounding tissue. This is different from the recent result of 1μg Fe/*g* tissue for about 0.75ppb susceptibility change reported by Wharton and Bowtell [2]. We examined the following possible explanations; size of the high pass filter/ threshold used in SWIM processing; presence of non-paramagnetic iron species; iron loading factor in ferritin; registration errors; presence of other magnetic materials; and tissue susceptibility difference (measured structure with respect to white matter without considering iron). Thresholding of 0.1 in SWIM processing caused about a 30% drop of susceptibility [2]. We used a 64x64 high pass filter which may cause about 50% susceptibility drop at the edge of the putman and caudate [5]. XRF measures total iron but it is assumed in susceptibility map of basal ganglia that all of the iron is in ferritin. Previous studies [6] from our laboratory have shown that different parts of the brain have similar iron coordination. As expected X-ray absorption spectra indicate that heme and ferritin are the abundant iron species. The most obvious anomaly that still requires explanation is that the internal capsule had high negative susceptibility that does not correlate with iron content. XRF showed that the internal capsule had the same total iron as the rest of the white matter. A negative internal capsule was also noticed by Wharton and Bowtell [2]. Iron loading factor of ferritin at these structures is a factor that remains to be explored.

Conclusion. We assumed that ferritin was the dominant iron species in putamen and caudate and estimated the relationship between SWIM susceptibility and iron concentration, for the first time on a voxel by voxel basis. This provides a major advance in noninvasive and safe estimation of iron in human brain tissue *in vivo* using susceptibility mapping.

Acknowledgments. The authors would like to thank Sam Webb at the Stanford Synchrotron Radiation Lightsource and Angela Auriat at the Dept. of Neurosurgery, Stanford University for their help in collecting XRF data. This work is supported by Heart and Stroke Foundation of Canada (HSFC) and the Canadian Institutes of Health Research (CIHR) - Institute of Circulatory and Respiratory Health, Clinical Imaging Initiative (FRN - 99472) to HN.

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