Quantitative Magnetic Susceptibility Mapping in Prodromal Huntington's Disease Subjects

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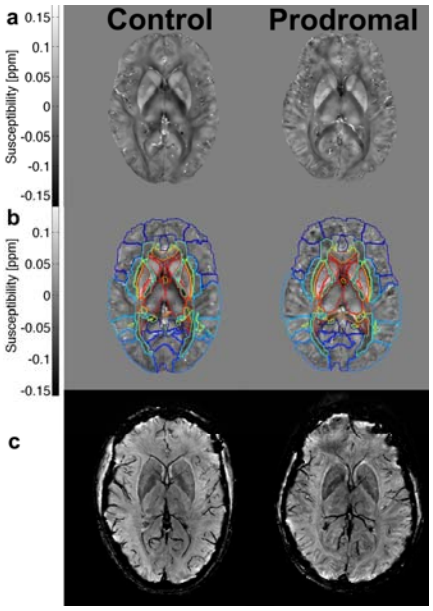

Figure 1: (a) QSM from 44 y/o control female and 44 y/o prodromal female subject; scale in ppm relative to CSF. (b) EvePM overlaid on QSM. (c) Qualitative SWI.

Target Audience: Researchers and clinicians interested in imaging of neurodegenerative disorders, especially Huntington's Disease, as well as imaging the brain using quantitative susceptibility mapping.

Purpose: Huntington's Disease (HD) is an autosomal dominant neurodegenerative disorder caused by an expansion of a CAG trinucleotide repeat in the *huntingtin* gene on chromosome 4. Onset is typically in middle age, with cognitive, motor, and psychiatric dysfunction, progressing to death over 15-20 years. Defining changes in HD brain prior to the onset of clinical disease is of critical importance for understanding disease pathogenesis and for monitoring the success of treatments designed to prevent or delay disease onset. Brain iron concentration is elevated in advanced HD, especially in the basal ganglia,[1] deep structures differentially affected in HD. The iron concentration of deep gray matter (GM) structures has been shown to correlate with magnetic susceptibility, as measured via Quantitative Susceptibility Mapping (QSM) methods.[2-4] We therefore hypothesized that QSM signal, reflecting iron concentration, would be elevated in prodromal individuals with the HD mutation who have not yet developed clinically diagnosable signs of HD. We applied QSM to an initial group of normal and prodromal HD subjects, using a QSM-based expansion of the Eve atlas from Johns Hopkins University, a single-subject human brain with 1mm^3 isotropic resolution in standard Montreal Neurological Institute (MNI) coordinates.[5] This allowed us to determine magnetic susceptibility differences between control and prodromal subjects with an automated approach. For comparison, we also processed qualitative susceptibility-weighted images (SWI),[6] in which GM structures with higher magnetic susceptibility appear more hypointense.

Methods: Three healthy control subjects (47 +/- 3.6 years of age, 3 female) and four prodromal HD subjects (44.5 +/- 2.5 years of age, two male, two female) were studied after IRB approval and written informed consent, using a 7T Philips MR system with a 32-channel NovaMedical head coil. Phase images were acquired using a 22-echo 3D gradient-recalled echo (GRE) sequence (SENSE = 2x1x2, TR = 61ms, TE_1 = 2ms, ΔTE = 2ms, $\alpha = 19^o$, Scan Duration = 6:13min). Imaging covered most of the cerebrum (80 slices, acquired isotropic resolution of 1.0mm^3. Using MATLAB, SWI images were processed with homodyne filtering of the phase signal from the eighth echo at TE=16ms. For QSM, the phase signal in each echo was processed with Laplacian-based phase unwrapping.[7] The frequency shift in Hertz was calculated from the linear slope of the phase as a function of TE using eight echoes. Slowly varying background gradients were removed from the resonance frequency map using dipole fitting,[8] and the susceptibility maps were calculated with MEDI.[9] For each subject, the outer surface of the brain was coregistered to the GRE Magnitude image of the Eve atlas with AIR,[10,11] and the internal brain structures were coregistered with dual-channel Large Deformation Diffeomorphic Metric Mapping (LDDMM)[12,13] using both the GRE magnitude and QSM images. The resulting transformation matrices were inverted, then applied to the EvePM, thereby transforming the ROIs into subject space. For each subject, deep white matter (WM) bundles were grouped into one reference ROI with an average susceptibility set to -0.03ppm, so that the average susceptibility in the more inhomogeneous ventricles would be approximately 0ppm. Brighter signal in the referenced QSM thus indicates structures more paramagnetic than CSF.

Results: Figure 1a shows example axial QSM images for a control and prodromal subject, both 44-year-old females. Figure 1b shows the regions of interest delineated by automated segmentation with the EvePM. Figure 1c shows qualitative non-referenced susceptibility-weighted images, in which relative hypointensity indicates a more paramagnetic susceptibility. Figure 2 displays the average magnetic susceptibility for six deep gray matter regions, comparing the control subjects to the prodromal subjects. Across all deep GM structures, the prodromal subjects showed a more positive susceptibility than in control subjects (p=0.009), possibly due to the presence of paramagnetic iron. A Welch's t-test comparing the average susceptibility per ROI showed significantly more paramagnetism in the prodromal subjects in the hippocampus (Fig. 2, **, p=0.003), as well as less significantly in the putamen (Fig. 2, *, p=0.05).

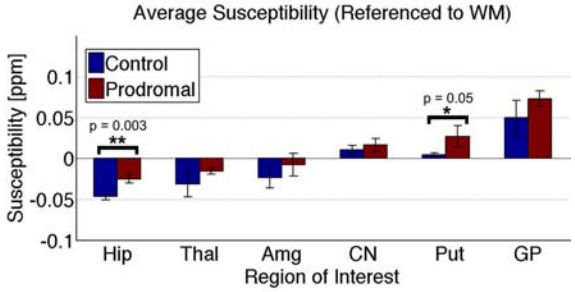

*Figure 2: Average susceptibility for prodromal subjects vs. age-matched controls for the hippocampus**, thalamus, amygdala, caudate nucleus, putamen*, and globus pallidus.*

Discussion: Brain iron concentration has been shown to increase in advanced HD.[1] Interestingly, iron also increases in the normal aging brain;[14] hence, comparison with age-matched controls is necessary. As shown in Figure 2, the overall average susceptibility in the deep GM regions of prodromal subjects is significantly more positive than in age-matched controls, especially in the hippocampus and putamen, which may indicate higher iron concentration before clinical symptoms arise. These data show that QSM may have potential as a noninvasive method to quantitatively track neurodegeneration in prodromal HD, but more studies are needed to solidify this theory. Variability as depicted by standard deviation in each brain region may reflect biological variation, especially given the small sample size, as well as any coregistration errors.

Conclusion: Coregistration and automated segmentation of the brain with the Eve atlas allowed efficient analysis of prodromal Huntington's Disease subjects and age-matched controls. These preliminary results demonstrate greater paramagnetic susceptibility in prodromal subjects than in age-matched controls, consistent with accumulation of iron before the onset of cognitive symptoms. QSM may provide an important measure of early change in the HD brain. **Funding:** NIH-P41 EB051909, NIH 5 T32 MH015330. **References:** 1) Bartzokis G, et al. Arch Neurol 1999:56,569. 2) Schweser F, et al. NeuroImage 2011:54,2789. 3) Bilgic B, et al. NeuroImage 2011:59,2625. 4) Langkammer C, et al. Radiology 2010:257,455. 5) Mori S, et al. Brain 2007:40,570. 6) Haacke EM. MRM 2004:52,612. 7) Li W, et al. NeuroImage 2011:55,1645. 8) de Rochefort L et al, MRM 2010:63,194. 9) Liu T, et al. MRM 2011:66,777. 11) Woods RP, et al. JCAT 1998:22,139. 12) Woods RP, et al. JCAT 1998:22,153. 13) Beg MF, et al. IJCV 2005:61,139. 13) Cao Y, et al. IEEE Trans Med Im 2005:24,1216. 14) Brass SD, et al. TMRI 2006:17,31.