MAGNETIC SUSCEPTIBILITIES MEASURED BY QUANTITATIVE SUSCEPTIBILITY MAPPING (QSM) INDICATE BRAIN IRON LEVELS CORRELATE WITH GENETIC BURDEN IN PRODROMAL HUNTINGTON'S DISEASE

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Introduction: Huntington's disease (HD) is caused by a cytosine-adenine-guanine (CAG)-repeat expansion in the *huntingtin* gene [1]. This expansion results in a protein with a long polyglutamine tract that has a toxic effect on neuronal populations of the central nervous system beginning years before overt clinical onset of the disease. The capacity to monitor disease progress before clinical onset will likely be critical for the development of therapeutic interventions, and will require sensitive and robust imaging-based biomarkers of toxicity. Post-mortem studies of advanced HD have shown increases of almost 150% in crude iron concentration in the putamen and globus pallidus [2]. It was recently shown that HD expansion mutation directly influences iron uptake [3]; therefore, iron might be a viable biomarker in early stages of the disease. The recent developments in the field of quantitative susceptibility mapping (QSM) have made it possible to directly map brain tissue magnetic susceptibility, which has been shown to correlate well with tissue iron concentration in several deep gray matter regions of the brain [4,5]. In the present study, QSM was used to assess the difference in iron levels between healthy controls and prodromal-HD patients, focusing on brain regions that have shown altered iron content in advanced HD. To assess its potential value as a biomarker, tissue magnetic susceptibility values were compared to the CAG-Age Product Scaled (CAPS) score, which is a strong marker of the extent of exposure to the effects of the expansion mutation and predictor of time to conversion to manifest HD.

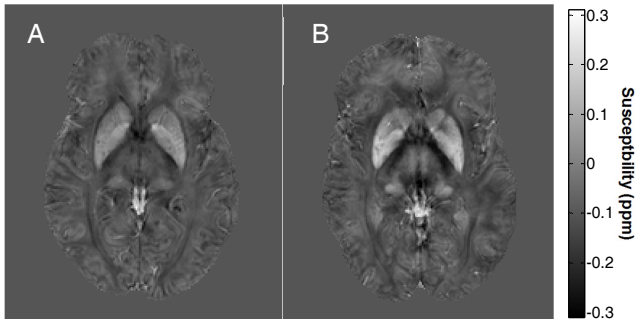

Fig. 1: *Comparison of a healthy (A) and prodromal-HD (B) shows increased susceptibility values in gray matter structures.*

Methods: Fifteen prodromal-HD subjects (5 male, 10 female; mean age 42.4 ± 8.7, with 40 or more CAG repeats) and sixteen healthy age-matched controls (8 male, 8 female; mean age 43.3 ± 11.7) were studied using a 7T Philips MR system with a 32-channel NovaMedical head coil. A T1-weighted MPRAGE image (TR/TE = 4.8ms/2.1ms; 0.6x0.6x0.6 mm^3) was acquired for anatomical referencing and automated image segmentation. For eight prodromal-HD subjects and all the normal controls, multi-echo 3D GRE scans with 10 echoes (TR/TE/ΔTE=68/4/2ms, flip angle=9°, 1x1x1mm^3) were acquired. For the other 7 patients, 3D GRE scans with 22 echoes (TR/TE/ΔTE=61/2/2ms, flip angle=19°, 1x1x1mm^3) were acquired. For all the GRE scans, phase datasets acquired with an echo time in the range of 10-18ms were used. Phase unwrapping was performed using Laplacian-based phase unwrapping [6]. Subsequently, background field were eliminated with sophisticated harmonic artifact reduction for phase data (SHARP) [7] using a variable spherical kernel size with a maximum radius of 4mm and a regularization parameter of 0.05 [8]. After removal of background field, the resulting images of all five echoes were averaged to obtain a higher signal to noise ratio as compared to single echo reconstruction [9]. Inverse dipole calculations to obtain the susceptibility maps were performed using an LSQR-based minimization [6]. The T1 image was co-registered to the GRE magnitude image using FSL FLIRT [10] and used for segmentation in a multi-atlas matching approach [5,11]. The central cerebral spinal fluid region (CSF) in the lateral ventricles was selected as a reference region for the final susceptibility quantification. All reported susceptibility values are relative to this reference region. In order to quantify the genetic burden at the time of the scan, the CAPs score was calculated per patient [12] as *CAPs = Age × (CAG–33.66)/432.33)*, which indicates a probability of disease onset within 5 years of <0.5, 0.5 and >0.5 for CAPs scores <1, 1 and >1, respectively.

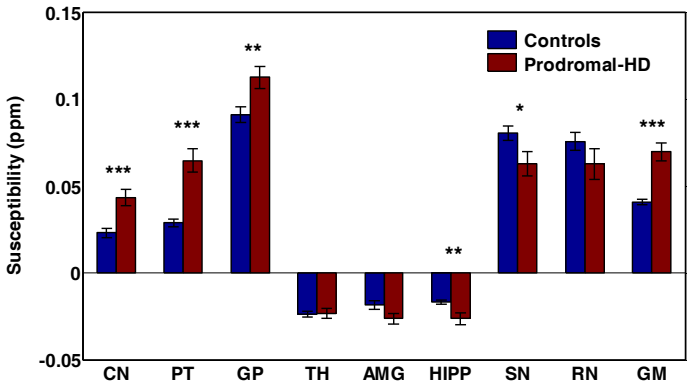

Fig. 2: *Average susceptibility values for deep gray matter structures are significantly different in prodromal-HD. CN = Caudate Nucleus, PT = Putamen, GP = Globus Pallidus, TH = Thalamus, AMG = Amygdala, HIPP = Hippocampus, SN = Substantia nigra, RN = Red Nucleus, GM = average of basal ganglia (CN, PT, GP, SN). * p< 0.05, ** p<0.01, *** p<0.001*

Results: Increased susceptibility values in deep gray matter structures were observed in prodromal-HD subjects. Example slices showing the basal ganglia of a healthy control and a prodromal-HD subject are shown in ***Fig. 1***. When controlling for age, significant increases were seen (***Fig. 2***) in the caudate nucleus (CN), putamen (PT), and globus pallidus (GP). Based on proportionality of gray matter susceptibility with iron content [4,5], these indicate an increase in iron. These findings are consistent with previous findings using magnetic field correlation [13] and field shift [14]. In the hippocampus (HIPP) and substantia nigra (SN), significant decreases were observed. The CAPs scores correlate with the average susceptibility (***Fig. 3***) in the caudate nucleus *(p = 0.04, r = 0.51)* and the putamen *(p = 0.001, r = 0.60)*. When included, age or structure volume did not have a significant contribution, indicating potential use of magnetic susceptibility based tissue iron measures as a biomarker for HD.

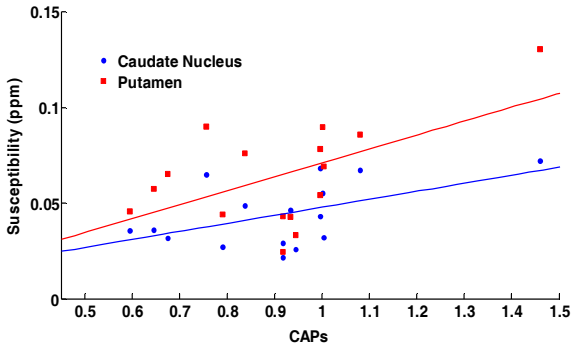

Fig. 3: *CAPs score and susceptibility correlated in CN and PT.*

Conclusion and Discussion: In the present study, measuring magnetic susceptibility showed significant differences in gray matter iron concentrations between prodromal-HD and control subjects, with clinical relevance indicated by the significant correlation between susceptibility and CAPs scores.

References: [1] Brandt J, et al. Neurology 1996;46:527. [2] Chen JC, et al. AJNR Am J Neuroradiol 1993;14:275. [3] Muller M, et al. J Neurochem 2014;130:328. [4] Langkammer C, et al. Neuroimage 2012;62:1593. [5] Lim IAL, et al. Neuroimage 2013;82:449. [6] Li W, et al. Neuroimage 2011;55:1645. [7] Schweser F, et al. Neuroimage 2011;54:2789. [8] Wu B, et al. Magn Reson Med 2012;67:137. [9] Wu B, et al. Neuroimage 2012;59:297. [10] Jenkinson M, et al. Neuroimage 2002;17:825. [11] Tang X, et al. PLoS One 2013;8:e65591. [12] Zhang Y, et al. Am J Med Genet B Neuropsychiatr Genet 2011;156B:751. [13] Dumas EM, et al. Neuroimage 2012;61:558. [14] Rosas HD, et al. Arch Neurol 2012;69:887. **Funding:** NIH P41 EB051909, NIH 5 T32 MH015330