Magnetic susceptibility in gray matter is associated with age-related neuropathology: An ex-vivo QSM study in a community cohort

Arnold Moya Evia Jr. [1], David A Bennett[2,3], Julie A Schneider[2,3], Aikaterini Kotrotsou[4], Robert J Dawe[2], and Konstantinos Arfanakis[1,2]

[1]*Illinois Institute of Technology, Chicago, Illinois, United States,* [2]*Rush Alzheimer's Disease Center, Illinois, United States,* [3]*Rush University Medical Center, Illinois, United States,* [4]*MD Anderson Cancer Center, Texas, United States*

INTRODUCTION: Iron accumulation in the brain has been linked to aging and various neuropathologies [1,2]. Measurement of iron in gray matter structures may aid in the development of biomarkers for these pathologies. Quantitative susceptibility mapping (QSM) can allow for the quantification of iron levels [3,4]. The purpose of this study was to investigate the neuropathologic correlates of magnetic susceptibility in gray matter throughout the brain for TDP43 pathology, hippocampal sclerosis, Alzheimer's Disease (AD).

METHODS:

Participants and Data Acquisition: Cerebral hemispheres were obtained from 53 participants (90 ± 7 years of age; 17 males) of the Rush Memory and Aging Project [5] and the Religious Orders Study [6], two longitudinal, epidemiologic clinical-pathologic cohort studies of aging. All hemispheres were submerged in 4% formaldehyde solution early after death, and were imaged with MRI approximately 30 days postmortem as shown in Figure 1. All MRI data was collected on the same 3T Philips MR system using: a 3D multi-echo gradient-echo sequence with 10 echoes (TE/deltaTE/TR = 4.6/4.63/49.5 ms, acquired voxel size = 1 mm^3) and a multi-echo fast spin-echo sequence with 5 echoes (TE/deltaTE/TR = 16.5/16.5/4055 ms, acquired voxel size = 0.6 mm^3). Following ex-vivo MRI, hemispheres underwent neuropathologic assessment by a board-certified neuropathologist blinded to all clinical and imaging findings.

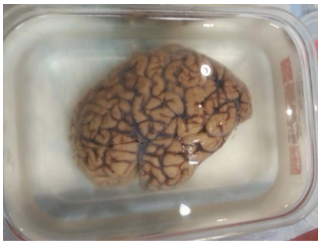

Figure 1. Photo of a participant's hemisphere submerged in formaldehyde in an imaging container

Processing and Analysis: To produce high quality susceptibility maps, voxels affected by air-tissue interfaces in the gradient-echo data were first masked out. Phase maps were generated and unwrapped using FSL PRELUDE [7], and frequency shift maps were produced by phase subtraction. The background field was removed by projection onto dipole fields [8]. QSM maps were created with a magnitude-weighted split Bregman L1 regularization algorithm [4]. The regularization parameter was selected as the value with the largest curvature on the L-curve, and was set to $9.2*10^{-4}$ for all participants. Spin-echo data was corrected for RF bias with FSL FIRST [9], and was used as the magnitude weight for the QSM algorithm. A reference value for each participant's susceptibility map was chosen as the mean of a 5x5x5 mm^3 volume inside the 4% formaldehyde solution. Gray matter regions for each participant's hemisphere were defined by using a multi-atlas segmentation approach, as described in another study [10]. For each region, linear regression was used to study the association of median susceptibility values with TDP43 pathology, AD, and hippocampal sclerosis, while controlling for age at death, sex, and postmortem interval to imaging. Statistical significance was set at $p<0.05$.

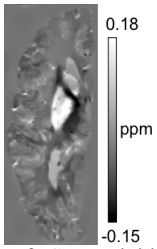

Figure 2. Susceptibility map of a participant's hemisphere

RESULTS: Susceptibility maps were successfully reconstructed for each subject, as seen in figure 2. Statistically significant positive correlations were detected between magnetic susceptibility values and measures of neuropathology in gray matter regions throughout the brain, and are depicted in figure 3. Correlation with TDP43 was found in the caudate ($p=0.009$). The putamen was correlated with AD ($p=0.02$) and hippocampal sclerosis ($p=0.01$).

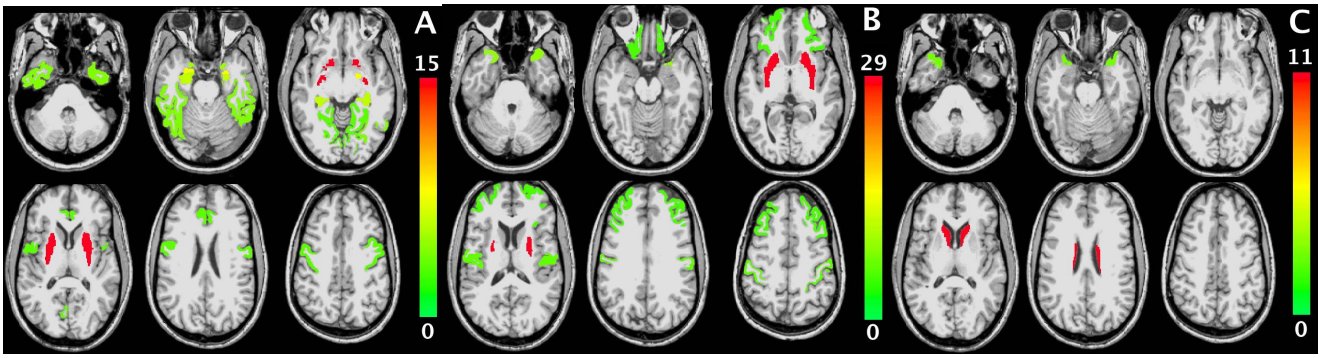

Figure 3. Gray matter regions with significant positive correlations between magnetic susceptibility and A) TDP43 pathology, B) AD, C) hippocampal sclerosis ($p<0.05$, uncorrected). Unique colors have been assigned to different model estimates (Units: ppb). Results are overlaid on a T1-weighted template.

DISCUSSIONS AND CONCLUSIONS: These findings suggest that magnetic susceptibility values in gray matter measured with QSM are sensitive to age-related neuropathology. The correlation of magnetic susceptibility with AD pathology in the putamen may be a result of iron accumulation due to disruption of brain iron homeostasis in AD [11]. The correlations of susceptibility in the caudate with TDP43 pathology, and in the putamen with hippocampal sclerosis are new findings and remain to be replicated in a larger sample. This study is ongoing and additional participants and neuropathologies are being added to the analysis. Nevertheless, the present study provides a strong indication that QSM may play an important role in the development of biomarkers for age-related neuropathology.

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