Magnetic susceptibility in subcortical gray matter is associated with Alzheimer's pathology: An ex-vivo QSM-pathology investigation in a community cohort
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TARGET AUDIENCE
Investigators conducting MRI research on quantitative susceptibility mapping and Alzheimer's disease.

PURPOSE
Iron accumulation in the brain has been associated with aging, and Alzheimer's disease (AD) [1]. MRI techniques that allow detection of iron accumulation may lead to development of biomarkers of AD pathology. Quantitative susceptibility mapping (QSM) was introduced recently, and is shown to be sensitive to changes in iron levels [2,3]. Therefore, the purpose of this study was to investigate the neuropathologic correlates of magnetic susceptibility in subcortical gray matter, by conducting the first ex-vivo QSM-pathology investigation of AD in a community cohort.

METHODS
Participants and Data Acquisition: Cerebral hemispheres were obtained from 48 participants (90 ± 6 years of age; 13 males) of the Rush Memory and Aging Project [4] and the Religious Orders Study [5], 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. 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 mm³) 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 mm³). Following ex-vivo MRI, hemispheres underwent neuropathologic assessment by a board-certified neuropathologist blinded to all clinical and imaging findings. A composite measure of global AD pathology was created from counts of neurofibrillary tangles, neuritic and diffuse plaques [6].

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 linear fitting across 3 echoes. The background field was removed by projection onto dipole fields [8]. QSM maps were created with a magnitude-weighted split Bregman L1 regularization algorithm [3]. 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. A reference value for each participant's susceptibility map was chosen as the mean of a 5x5x5 mm³ volume inside the 4% formaldehyde solution. The susceptibility maps from all participants were spatially normalized by non-linearly registering the first echo of the gradient-echo data to a template using the Automated Registration Toolbox (ART) [9], and then applying the corresponding transformations to the susceptibility maps. The putamen and caudate were outlined on the template and the outlines were superimposed onto the spatially transformed susceptibility maps. The median susceptibility value in each region was extracted for each participant. Linear regression was used in each region to investigate the link between susceptibility values and the composite measure of global AD pathology, controlling for age at death, sex, and postmortem interval to imaging. Statistical significance was set at p<0.05.

RESULTS & DISCUSSION
Statistically significant positive correlations were detected between magnetic susceptibility values and the composite measure of global AD pathology in the putamen (p=0.026) and caudate (p=0.009). These findings suggest that magnetic susceptibility values in subcortical gray matter measured with QSM are sensitive to AD pathology. 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 of AD pathology.