

T_2 alterations in ex vivo human brains with Alzheimer's disease pathology

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Introduction: One of the potential benefits of postmortem MRI of the human brain in research of aging and Alzheimer's disease (AD) is the ability to compare imaging findings to histopathologic data acquired at nearly the same point in time, minimizing the extent of microstructural changes that occur between imaging and histology. Therefore, postmortem MRI may provide a unique opportunity for directly evaluating the ability of new MRI techniques to detect tissue changes due to AD and other neurodegenerative diseases. The purpose of this work was to investigate differences in T_2 relaxation times among postmortem brain specimens with low, intermediate, and high likelihood of AD, assessed histopathologically, according to the National Institute on Aging (NIA)-Reagan Institute criteria [1].

Methods: After death and rapid autopsy, one cerebral hemisphere from each of 80 elderly subjects was immersed in 4% formaldehyde solution and stored at 4° C. After approximately two months of fixation (mean = 59.8 days, range = 22 to 179 days), each hemisphere was removed from refrigeration and scanned at room temperature using a 3.0-T GE MR imager (General Electric, Waukesha, WI). A 2D fast spin echo sequence with two echo-times was used to acquire proton density (PD) weighted and T_2 -weighted images, in sagittal slices through the hemispheres, with $TE_1 = 13.0$ ms, $TE_2 = 52.0$ ms, and true resolution of $0.625\text{ mm} \times 0.625\text{ mm} \times 1.5\text{ mm}$. Left hemispheres were mirrored to appear as right hemispheres. Using a high-dimensional warping algorithm (Automatic Registration Toolbox), the PD-weighted volumes were spatially normalized to a population-based, postmortem template that was specially created for this purpose. The recorded deformations were then applied to T_2 volumes calculated from the original PD- and T_2 -weighted images. Following postmortem imaging, the hemispheres were histologically examined for AD pathology, using NIA-Reagan criteria for low ($n=34$), intermediate ($n=25$), or high likelihood for AD ($n=21$). Finally, voxelwise analysis of covariance (ANCOVA) was performed in order to test if changes in T_2 are associated with the NIA-Reagan score. Covariates included the subjects' age at death and the time interval between death and postmortem imaging. Results for a given voxel were considered to be statistically significant when $p < 0.01$, and the voxel was part of a cluster with a volume larger than 0.25 cm^3 .

Results: In regions around the anterior and posterior horns of the lateral ventricle, T_2 times were elevated by 5-15 ms in the high likelihood of AD group compared to the low likelihood group (Fig. 1A,B,C, orange color). T_2 times were also elevated in subcortical white matter in the frontal and parietal lobes (Fig. 1D, orange color). In and around the medial aspect of the putamen and globus pallidus, T_2 times were depressed by 5-10 ms in the high likelihood group compared to the low likelihood group (Fig. 1 A,B,D, blue color). Similar but smaller T_2 differences were observed between the high and intermediate likelihood groups, and between the intermediate and low likelihood groups. Finally, T_2 times increased significantly with both age and postmortem time to imaging in different locations throughout the brain hemispheres (results not shown). Tissue located deep within the hemispheres, far from the surface, was most affected by the postmortem interval, in agreement with a previously published longitudinal study [2].

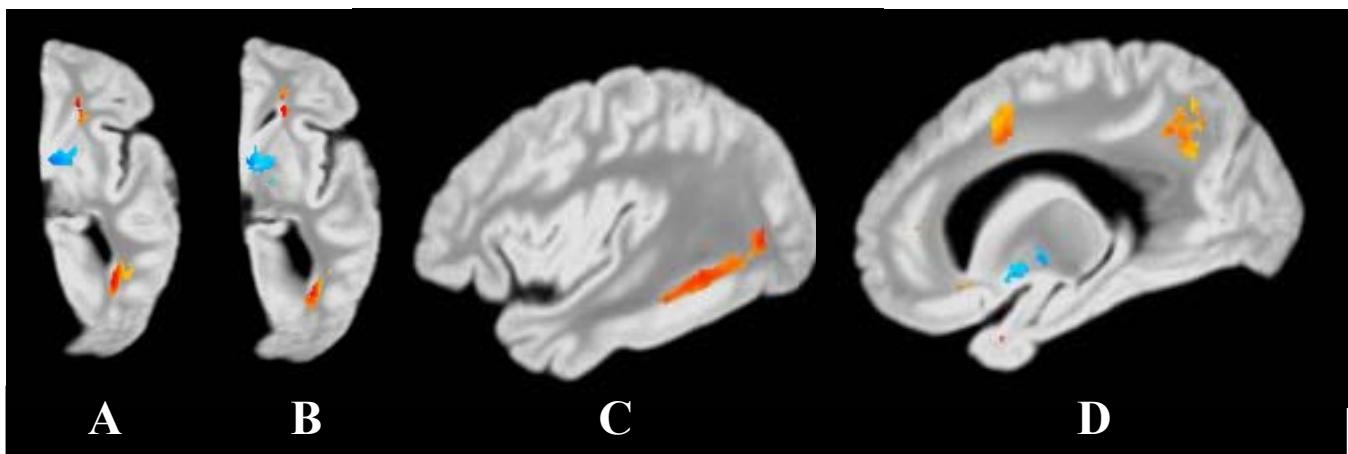


Figure 1. Regions where T_2 is significantly ($p < 0.01$) elevated (orange) or depressed (blue) in Alzheimer's disease subjects compared to non-Alzheimer's subjects (NIA-Reagan criteria for high likelihood vs. low likelihood of AD). A and B: axial views of the postmortem hemisphere template. C and D: sagittal view of the template.

Discussion: Substantial differences in T_2 times were observed in hemispheres with low compared to high likelihood of AD, assessed by NIA-Reagan criteria. These differences may be related to AD pathology; alternatively, as seen in antemortem MRI, the increased T_2 in white matter may be related to coexisting vascular disease [3], and the reduced T_2 in the globus pallidus and putamen may be related to coexisting ferritin iron accumulation [4]. A comprehensive neuropathologic-imaging investigation is currently underway to directly assess the pathologic changes underlying these observed T_2 changes.

References: [1] Newell K, et al. J Neuropathol Exp Neurol 1999;58:1147-1155. [2] Dawe RJ, et al. Magn Reson Med 2009;61:810-818. [3] DeCarli C, et al. Stroke 2005;36:50-55. [4] Bartzokis G, et al. Arch Gen Psychiatry 2000;57:47-53.