# Postmortem MRI Reveals Alterations in $T_2$ Associated with Histopathologically Verified Alzheimer's Disease and other Pathology in the Elderly Human Brain

Robert Dawe[1], Julie Schneider[1], David Bennett[1], and Konstantinos Arfanakis[1,2]

[1]*Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, IL, United States,* [2]*Department of Biomedical Engineering, Illinois Institute of Technology, Chicago, IL, United States*

## Introduction

Alterations in the transverse relaxation time constant, $T_2$, related to Alzheimer's disease (AD) have been observed in different regions of the brain [1,2], but the majority of studies investigating this phenomenon did not have the benefit of a pathological diagnosis of AD, instead relying only on clinical diagnosis. The purpose of this study was to conduct a cerebrum-wide exploratory analysis of $T_2$ alterations associated with histopathologically confirmed AD, while also accounting for the effects of other types of neuropathology that are common in the elderly.

## Methods

We employed postmortem MRI in order to obtain $T_2$ measurements and corresponding pathology data from a large number (n=228) of elderly subjects enrolled in either the Rush Memory and Aging Project or the Religious Orders Study [3]. After being stored in 4% formaldehyde solution at 4° C for an average of 52 days, each brain hemisphere was imaged at room temperature using a clinical 3.0-T MRI scanner and a fast spin echo sequence with the following parameters: 0.625 × 0.625 × 1.5 $mm^3$ resolution, TEs of 13 ms and 52 ms, TR of 3.8 s, and total scan time of 30 minutes. $T_2$ maps were calculated from the early and late TE images and were non-linearly warped to a study-specific template. Histopathologic examination was performed by a board-certified neuropathologist using established guidelines to identify AD pathology (meeting NIA-Reagan criteria for low, intermediate, or high likelihood of AD), cerebral amyloid angiopathy, Lewy bodies, gross infarcts, microscopic infarcts, and hippocampal sclerosis. Voxelwise analysis of covariance (ANCOVA) was then carried out, first considering each type of pathology separately and then considering multiple types of pathology simultaneously. In the adjustment for multiple comparisons, a false discovery rate of 5% was accepted (http://www.fmrib.ox.ac.uk/fsl/randomise/fdr.html) and clustering was also employed (min. cluster size = 100 $mm^3$).

## Results

When considered individually, the neuropathologies that were associated with significant $T_2$ alterations were AD (meeting NIA-Reagan criteria for high likelihood of AD versus low likelihood), multiple gross infarcts per hemisphere (as opposed to none or only one), and hippocampal sclerosis. In a combined ANCOVA that simultaneously considered each of these three types of pathology, AD was associated with significant $T_2$ prolongation, primarily in the white matter of the frontal, parietal, and temporal lobes (Fig. 1). Multiple gross infarcts were associated with widespread $T_2$ prolongation throughout much of the white matter (Fig. 2). Hippocampal sclerosis was not found to be associated with any significant regions of $T_2$ alterations in this combined ANCOVA.

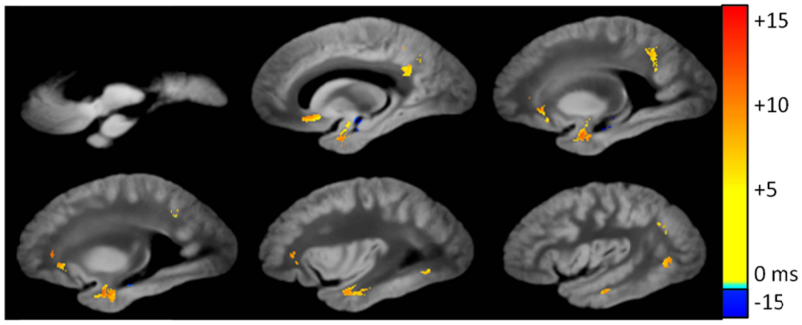


**Figure 1.** Color-coded regions of significant $T_2$ alterations associated with Alzheimer's disease (NIA-Reagan high likelihood).

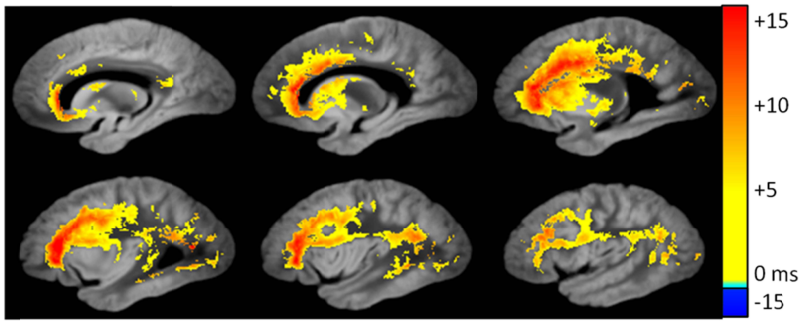


**Figure 2.** Color-coded regions of significant $T_2$ alterations associated with multiple gross infarcts per brain hemisphere.

## Discussion

Based on the current findings and supporting DTI evidence from the literature [4], we surmise that the AD-related $T_2$ prolongation in white matter is brought about by pathologic processes which ultimately lead to an increase in the tissue's free water content (e.g. neuronal loss or demyelination). The regions exhibiting AD-related $T_2$ prolongation have been implicated in AD literature. The underlying cause of $T_2$ prolongation associated with gross infarcts is almost certainly the replacement of necrotic tissue with free, unbound water molecules in the form of interstitial fluid. Immediate translation of these postmortem findings to the in vivo case is hampered by the uncertain relationship between antemortem and postmortem $T_2$ values, largely due to $T_2$ alterations brought about by death and chemical fixation. Nevertheless, this study demonstrates the utility of postmortem $T_2$ mapping of the human brain and, in doing so, provides candidates for MRI-based biomarkers of disease.

References [1] Arfanakis et al. (2007). *Brain Im Behav* 1(1-2), 11-21. [2] Wang et al. (2004). *Neurosci Lett* 363(2), 150-153. [3] Bennett et al. (2006). *Neurology* 66(12), 1837-1844. [4] Bozzali et al. (2011). *HBM* in press.