

Ex-vivo MRI Detects T₂ Alterations Associated with Alzheimer's Disease, Comorbid Neuropathology, and Antemortem Cognition

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Target Audience: Researchers in MRI of Alzheimer's disease and aging.

Purpose: Alterations in the transverse relaxation time constant, T₂, 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 voxelwise analysis of T₂ alterations associated with histopathologically confirmed AD and comorbid pathology, and also to investigate whether T₂ alterations are associated with cognitive impairment beyond that accounted for by the observed neuropathology.

Methods: In a period of 49 months, 211 elderly individuals (89.6 ± 6.6 y.o.) who participated in one of two longitudinal studies of aging died and were included in the current investigation. Participants had undergone testing within approximately one year of death to assess cognition in five domains: episodic, semantic, and working memory, perceptual speed, and visuospatial ability.³ After rapid autopsy, one cerebral hemisphere from each subject was immersed in 4% formaldehyde and refrigerated. After approximately two months of fixation, hemispheres were scanned at 3T. A fast spin echo sequence was used to acquire proton density- and T₂-weighted sagittal slices with the following parameters: FOV 16 × 16 cm², matrix 256 × 256, 0.6 × 0.6 × 1.5 mm³ resolution, multiple TEs between 13-83 ms, TR of 4 s, and total scan time of 30 minutes. Calculated T₂ maps were normalized via high dimensional warping to a study specific template.⁴ Histopathologic examination was then performed using established guidelines to identify AD pathology, cerebral amyloid angiopathy, Lewy bodies, gross infarcts, microscopic infarcts, and hippocampal sclerosis.⁵ Voxelwise analysis of covariance (ANCOVA) was carried out with T₂ as the outcome variable and the six types of pathology as explanatory variables, while controlling for subject age, sex, education, and hemisphere side. A similar analysis was carried out with cognition as the outcome and demographics, pathology, and T₂ as explanatory variables. Results were adjusted for multiple comparisons by allowing a false discovery rate of 5% (<http://www.fmrib.ox.ac.uk/fsl/randomise/fdr.html>), along with clustering (min. cluster volume = 0.1 cm³).

Results: In ANCOVA simultaneously considering all 6 types of neuropathology, AD was associated with significant T₂ prolongation, primarily in white matter of the frontal, parietal, and temporal lobes (Fig. 1A). Multiple gross infarcts were associated with widespread T₂ prolongation throughout white matter (signals from fluid were not included in this analysis) (Fig. 1B). For voxelwise ANCOVA in which cognition was modeled as a function of T₂ and neuropathologic indices, reduced performance in the semantic memory and working memory domains was associated with prolonged T₂ in white matter of the frontal lobe (Fig. 2). In secondary analyses, these clusters of T₂ prolongation explained an additional 8.7 percent of the variance in semantic memory and an additional 10.1 percent of the variance in working memory, on top of that explained by demographics and observed pathology.

Discussion and Conclusion: To our knowledge, this study represents the first cerebrum-wide analysis of T₂ effects associated with the histopathology of AD and other types of pathology commonly found in the elderly human brain. The AD-related T₂ prolongation in white matter may be brought about by pathologic processes which ultimately lead to an increase in the tissue's free water content (e.g. neuronal loss or demyelination).⁶ The underlying cause of T₂ prolongation associated with gross infarcts may be the replacement of necrotic tissue with free, unbound water molecules in the form of interstitial fluid.⁷ In addition, findings regarding associations between cognition and prolonged T₂ suggest potential clinical relevance of detected T₂ alterations in brain tissue. There is evidently some type of pathologic phenomenon that is incompletely captured by current histopathologic examination methods, yet contributes substantially to cognition. Translation of these findings to the in vivo case is a necessary next step of this research.

References: 1. Bartzokis et al. *Arch Neurol.* 2003;60(3):393-398. 2. House MJ et al. *AJNR Am J Neuroradiol.* 2006;27(2):430-439. 3. Bennett et al. *Neurology.* 2006;66(12):1837-1844. 4. Ardekani BA et al. *J Neurosci Methods.* 2005;142(1):67-76. 5. Schneider JA et al. *Ann Neurol.* 2009;66(2):200-208. 6. West MJ et al. *Lancet.* 1994;344(8925):769-772. 7. Auriel E et al. *Acta Neurol Scand.* 2011;123(1):41-47.

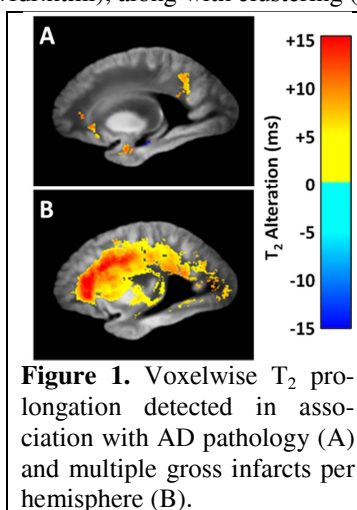


Figure 1. Voxelwise T₂ prolongation detected in association with AD pathology (A) and multiple gross infarcts per hemisphere (B).

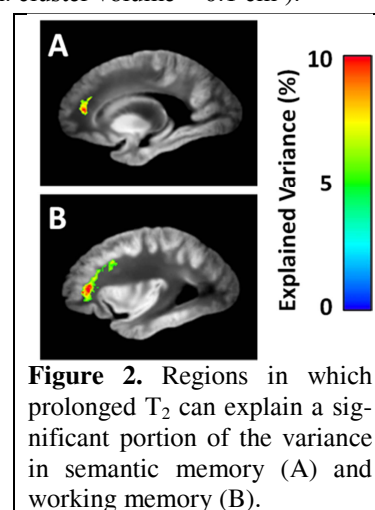


Figure 2. Regions in which prolonged T₂ can explain a significant portion of the variance in semantic memory (A) and working memory (B).