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Ex vivo T_2 relaxation: associations with age-related neuropathology and cognition

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ABSTRACT

The transverse relaxation time constant, T_2, is sensitive to brain tissue's free water content and the presence of paramagnetic materials such as iron. In this study, ex vivo magnetic resonance imaging was used to investigate alterations in T_2 related to Alzheimer's disease (AD) pathology and other types of neuropathology common in old age, as well as the relationship between T_2 alterations and cognition. Cerebral hemispheres were obtained from 371 deceased older adults. Using fast spin-echo imaging with multiple echo times, T_2 maps were produced and warped to a study-specific template. Hemispheres underwent neuropathologic examination for identification of AD pathology and other common age-related neuropathologies. Voxelwise linear regression was carried out to detect regions of pathology-related T_2 alterations and, in separate analyses, regions in which T_2 alterations were linked to antemortem cognitive performance. AD pathology was associated with T_2 prolongation in white matter of all lobes and T_2 shortening in the basal ganglia and insula. Gross infarcts were associated with T_2 prolongation in white matter of all lobes, and in the thalamus and basal ganglia. Hippocampal sclerosis was associated with T_2 prolongation in the hippocampus and white matter of the temporal lobe. After controlling for neuropathology, T_2 prolongation in the frontal lobe white matter was associated with lower performance in the episodic, semantic, and working memory domains. In addition, voxelwise analysis of in vivo and ex vivo T_2 values indicated a positive relationship between the two, though further investigation is necessary to accurately translate findings of the present study to the in vivo case.

1. Introduction

The transverse relaxation time constant, T_2, describes the decay rate of the transverse component of magnetization because of irreversible dephasing, and is one of the main sources of contrast available in magnetic resonance imaging (MRI). For H1 imaging at a given field strength, T_2 is influenced by a number of factors, including the ratio of free to myelin-bound water molecules (House et al., 2006), and the presence of paramagnetic molecules, such as the iron-laden compounds ferritin and hemosiderin (Haacke et al., 2005). Various types of pathology can alter these tissue properties and consequently change the T_2 values. For this reason, T_2 has the potential to serve as a biomarker for a range of diseases, and studies that investigate the relationships between pathology, cognition, and T_2 are warranted.

Alzheimer's disease (AD) is one such condition for which T_2 alterations have been observed in different regions of the brain. Several studies have reported a significant increase in hippocampal T_2 in individuals with AD compared with control subjects (Arfanakis et al., 2007; Kirsch et al., 1992; Laakso et al., 1996; Wang et al., 2004), and this is thought to be attributable to neuronal loss (West et al., 1994) and a resulting increase in the tissue's water content. However, other studies that examined the hippocampus did not find significant alterations in T_2 in individuals with mild to severe cognitive impairment (House et al., 2006) or in histopathologically confirmed cases of AD (House et al., 2008). Outside the hippocampus, elevated T_2 times have

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been reported in the internal capsule and in the frontal, temporal, and parahippocampal white matter of individuals with clinically or pathologically diagnosed AD and those with memory complaints or mild to severe cognitive impairment, a phenomenon which some attribute to the breakdown of myelin and the resultant increase in the tissue's free water content (Bartzokis et al., 2003; Besson et al., 1992; House et al., 2006). T_2 prolongation has also been reported in the amygdala of individuals with AD (Wang et al., 2004). Significantly reduced T_2 times thought to result from iron accumulation have been detected in the temporal lobe gray matter of living individuals reporting memory loss (House et al., 2006). By contrast, a related study of postmortem brain tissue did not find a significant T_2 reduction in the temporal lobe gray matter in histopathologically confirmed cases of AD (House et al., 2008).

Although these findings shed light on a potentially important relation of T_2 to AD, most of the studies did not have the benefit of a neuropathologic index or diagnosis of AD, and instead relied only on clinical diagnosis. Even in those few studies that combined measurements of T_2 with pathologic diagnosis of AD, common coexisting age-related pathologies, such as infarcts, were rarely included in the analyses. Further, we are not aware of prior studies that have examined the clinical significance of T_2 alterations by investigating their relation to cognitive status proximate to death, while also controlling for the effects of pathology. Therefore, several gaps in our knowledge of T_2 alterations related to AD and other common neuropathologies in the human brain remain to be filled.

To address these issues, it is necessary to combine clinical data with neuropathology and imaging data from the same human brain tissue via one of two methods. One approach involves conducting MRI during life, and then, upon death of those individuals, examining the brain tissue histopathologically. The other approach, the one adopted in the present study, avoids a potentially lengthy delay between MRI and death by subjecting ex vivo human brain specimens to MRI, followed by histopathologic examination. This second approach eliminates the possible confound of additional neuropathology formation between MRI and histopathologic examination, because both procedures are performed postmortem. It also permits assessment of the large number of cerebral hemispheres necessary to examine the range of pathologies across the spectrum of cognitive function.

The purpose of this study was to conduct a cerebrum-wide analysis of T_2 alterations associated with AD pathology, Lewy bodies, microscopic infarcts, gross infarcts, and hippocampal sclerosis (HS). We also investigated whether T_2 alteration is associated with cognitive function beyond that accounted for by neuropathology. The investigations were carried out by using ex vivo MRI to map T_2 values in human cerebral hemispheres from nearly 375 individuals, followed by histopathologic examination of the same specimens. All brain hemispheres were obtained from study participants whose cognition had been assessed proximate to death. By accounting for the aforementioned types of neuropathology in a combined multiple linear regression, it was possible to study the T_2 alterations associated with each condition, something that has not been accomplished previously in either region of interest (ROI)-based or voxel-based analyses. Additional voxelwise regression was carried out to assess the contribution of T_2 to variation in cognitive measures, while also considering the association of cognition with neuropathologic indices.

2. Methods

2.1. Ethics statement

Older adults included in this work were participants in either of two longitudinal clinical-pathologic studies of aging: the Rush Memory and Aging Project (MAP) or the Religious Orders Study (ROS) (Bennett et al., 2012a, 2012b). All participants provided written informed consent and signed an anatomic gift act. The study was approved by the Institutional Review Board of Rush University Medical Center.

2.2. Brain hemispheres

In a period of 6 years, 395 individuals from the MAP and ROS projects who died were considered for inclusion in this study. After a participant's death, autopsy technicians removed and separated the cerebral hemispheres as previously described (Dawe et al., 2011). One hemisphere per participant was selected for ex vivo imaging, and this hemisphere was immersed in phosphate-buffered 4% formaldehyde solution (prepared from paraformaldehyde) and refrigerated at 4 °C in a sealed plastic container within an hour of its removal from the skull.

2.3. Ex vivo image acquisition and processing

MRI scans occurred at 47 ± 25 days (mean ± standard deviation) postmortem (range 22–235 days) (Dawe et al., 2009). All scans were performed with the hemisphere immersed in room temperature formaldehyde solution in a clear, sealed acrylic container. Because of the ongoing nature of this imaging study, three different scanners were used to acquire fast spin-echo MRI data with at least two different echo times (TEs): a General Electric Signa scanner (Waukesha, WI, USA) was used from 2006 to 2008, a Siemens Trio (Erlangen, Germany) from 2008 to 2010, and a Philips Achieva (Best, The Netherlands) after 2010. While all 3 scanners had the same nominal field strength (3 Tesla) and approximately the same scan time (31–35 minutes), other factors

Table 1
Fast spin-echo sequences from each of 3 MRI scanners employed in the present study

	GE Signa 3T	Siemens Trio 3T	Philips Achieva 3T
Subjects scanned	95	88	188
FOV (mm)	160 × 160	160 × 160	160 × 160
Acquisition matrix	256 × 256	256 × 256	260 × 258
Slice thickness (mm)	1.5	1.5	1.5
Native voxel dimensions (mm)	0.625 × 0.625 × 1.5	0.625 × 0.625 × 1.5	0.615 × 0.620 × 1.5
Native voxel volume (mm^3)	0.59	0.59	0.57
Echo times (ms)	13, 52	12, 35, 58	16.5, 33, 49.5, 66, 82.5
TR (ms)	3600	3750	4055
ETL	6	2	5
NEX	6	4	2
Scan time (min)	31	32	35

Key: ETL, echo train length; FOV, field of view; MRI, magnetic resonance imaging; NEX, number of excitations; TR, repetition time.