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Insights into brain microstructure from the T_2 distribution

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Abstract

T_2 weighting is particularly sensitive, but notoriously unspecific, to a wide range of brain pathologies. However, careful measurement and analysis of the T_2 decay curve from brain tissue promise to provide much improved pathological specificity. In vivo T_2 measurement requires accurate 180 pulses and appropriate manipulation of stimulated echoes; the most common approach is to acquire multiple echoes from a single slice. The T_2 distribution, a plot of component amplitude as a function of T_2, can be estimated using an algorithm capable of fitting a multi-exponential T_2 decay with no a priori assumptions about the number of exponential components. T_2 distributions from normal brain show peaks from myelin water, intra/extracellular water and cerebral spinal fluid; they can be used to provide estimates of total water content (total area under the T_2 distribution) and myelin water fraction (MWF, fractional area under the myelin water peak), a measure believed to be related to myelin content. Experiments on bovine brain suggest that magnetization exchange between water pools plays a minor role in the T_2 distribution.

Different white matter structures have different MWFs. In normal white matter (NWM), MWF is not correlated with the magnetization transfer ratio (MTR) or the diffusion tensor fractional anisotropy (FA); hence it provides unique information about brain microstructure. Normal-appearing white matter (NAWM) in multiple sclerosis (MS) brain possesses a higher water content and lower MWF than controls, consistent with histopathological findings. Multiple sclerosis lesions demonstrate great heterogeneity in MWF, presumably due to varying myelin contents of these focal regions of pathology. Subjects with schizophrenia were found to have significantly reduced MWF in the minor forceps and genu of the corpus callosum when compared to controls, suggesting that reduced frontal lobe myelination plays a role in schizophrenia. In normal controls, frontal lobe myelination was positively correlated with both age and education; this result was not observed in subjects with schizophrenia.

A strong correlation between MWF and the optical density from the luxol fast blue histological stain for myelin was observed in formalin-fixed brain, supporting the use of the MWF as an in vivo myelin marker.

Keywords: Brain microstructure; Myelin water fraction; T_2 Distribution

1. Introduction

T_2 plays a role in almost every aspect of medical magnetic resonance. From the early days, it was clear that clinical T_2-weighted images were exquisitely sensitive to brain pathology, giving rise to much optimism that T_2 relaxation would lead to pathological specificity. However, in spite of a great deal of research, pathological specificity from T_2 was not realised [1] for a number of reasons; the most important being that conventional MRI techniques like proton density, T_1 and T_2 weighting are qualitative in a clinical setting.

The most specific MR techniques are tuned solely to study the spin species of interest. For example, in ^{1}H MR spectroscopy the signals from individual brain metabolites (<0.1% of the total signal) can be measured by using water suppression and taking advantage of the chemical shift. In fMRI, the signal from capillary blood (approximately 4% of

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the grey matter volume) can be separated from that of other tissue water by virtue of changes in blood T_2* caused by oxygenation changes.

The total ^{1}H magnetic resonance signal from brain includes contributions from protons in water as well as nonaqueous protons in molecules such as lipids, proteins and nucleic acids. The signal of water in tissue has T_2 times longer than 10 ms, while the nonaqueous proton signal decays to zero in less than 100 μs due to large unaveraged dipolar couplings between adjacent protons [2–4]. Consequently, it is relatively easy to measure the MR signal from water in brain with no contamination from the fast decaying nonaqueous tissue signal.

Pure water has a T_2 of about 3 s. Water in brain undergoes much faster T_2 relaxation rates; the degree of T_2 shortening depending on interactions between water and nonaqueous tissue. A homogeneous volume, such as a glass of pure water, gives rise to monoexponential T_2 relaxation. However, brain tissue is inhomogeneous, not only at the grey/white matter spatial level of 1 to 100 mm, but also at the cellular spatial level on the order of 1 to 10 μm. Furthermore, due to Brownian motion, water moves several micrometers each millisecond due to self-diffusion.

Pathological changes observed in neurodegenerative diseases include edema (increased intra- or extracellular water), blood–brain barrier breakdown (tight junction leakage), inflammation (proliferation of inflammatory cells), demyelination (breakdown of the myelin sheath), gliosis (proliferation of glial cells) and axonal loss (breakdown of the axon). The extent to which these pathologies can be distinguished by MRI depends upon whether they have a unique impact on the proton NMR signal; if these pathological changes affect the organisation of nonaqueous molecules in cellular structures, water T_2 relaxation should also be affected. It is therefore very challenging to relate T_2 relaxation directly to brain microstructure. A model for T_2 relaxation in brain must take into account both tissue architecture and the extent of water diffusion over the relevant timescales.

This review discusses how in vivo T_2 relaxation can provide specific information about brain anatomy and pathology. There is particular emphasis on T_2 relaxation pulse sequences and analysis techniques, on the interpretation of T_2 components as water reservoirs, as well as comparisons with results from other nonconventional MR techniques. Results are presented from normal volunteers and people with multiple sclerosis (MS) and schizophrenia.

2. In vivo T_2 measurement

The first step in a T_2 study of brain is the acquisition of a high-fidelity T_2 decay curve. The most common approach is to collect multiple echoes in a single MR sequence. Poon and Henkelman [5] developed a single slice multi-echo pulse sequence, employing composite radiofrequency pulses and gradient crusher pulses, which produces very good decay curves from brain. Key issues for accurate in vivo T_2 decay measurement are maintaining perfect 180 pulses in the presence of inhomogeneous B_1 and B_0 fields, and elimination of all contributions from stimulated echoes accruing from signal excited outside the selected slice. For quantitative analysis, T_2 decay curves must have high signal-to-noise ratios with the minimum acceptable noise standard deviation being about 1% of the signal strength at the shortest echo time [6]. The echo spacing should ideally be as short as feasible and the echo train length should be such that the last echoes report only noise. For in vivo human brain studies, the echo spacing should be 10 ms or less, and the echo train should exceed 1 s to measure the shortest T_2 components and to be sensitive to T_2 times on the 400-ms timescale, respectively. Unfortunately, the number of echoes acquired is often limited by considerations of power deposition and MR scanner pulse programmer restrictions. In the presence of microscopic magnetic field gradients, such as those caused by ferromagnetic or paramagnetic constituents, the shape of the T_2 decay curve depends upon the echo spacing [7]. Most of our in vivo T_2 decay curve results have been acquired from 32 echoes with a 10-ms echo spacing [8–10]. More recently, we have collected 32 echoes at 10-ms spacing plus a further 16 echoes with an echo spacing of 50 ms [11].

3. T_2 decay curve analysis

Fig. 1 shows several T_2 decay curves from normal human brain. Different white and grey matter structures decay at dissimilar rates. Furthermore, different brain pathologies have been observed to give rise to unique decay curves. The semi-logarithmic T_2 plots are not well fit

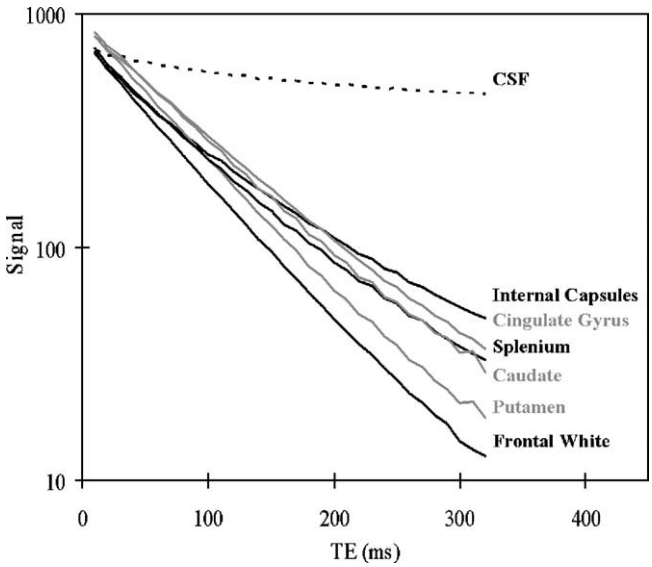

Fig. 1. T_2 decay curves for various white (black line) and grey (grey line) matter structures, as well as CSF (dashed line).