Indirect MRI Detection of Myelin Water Based on Water Exchange Properties

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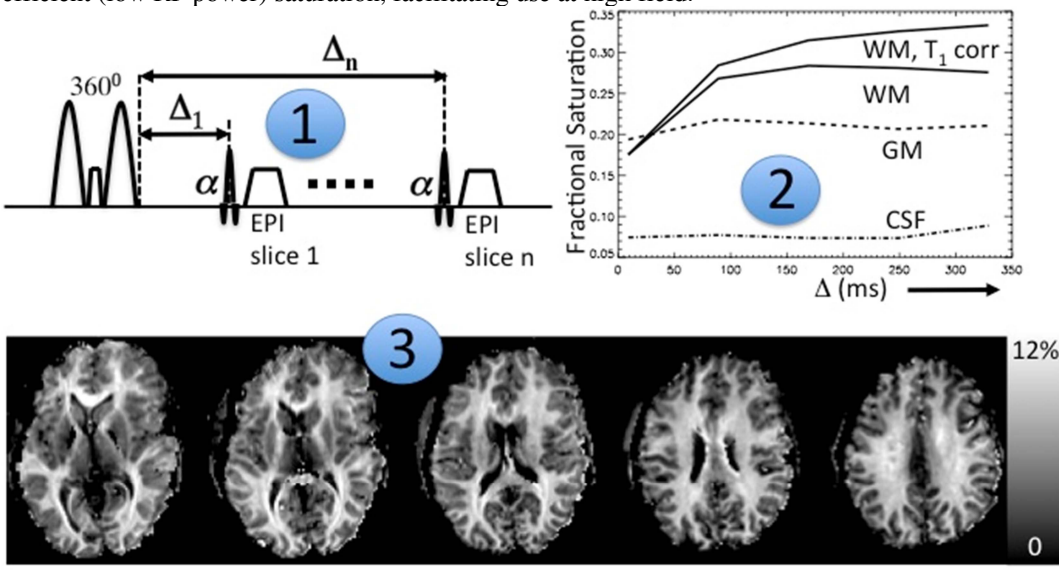
Purpose: Quantitative measurement of brain myelin content has been one of the longstanding goals of MRI, as it may inform on the level of disease activity and the effectiveness of treatment protocols in demyelinating diseases such as multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS). There are various MRI approaches to indirectly detect the presence of myelin, based on its effect on T_1, T_2, or T_2^* relaxation (1-7), or magnetization transfer (8-12). However, widespread clinical application of these methods is hampered by limitations in sensitivity or specificity. Here, we describe a novel approach that may overcome these issues.

Methods: The method is based on a saturation transfer (ST) approach introduced previously (13) and the observation that water trapped between myelin layers ("myelin water, MW") exchanges relatively slowly with other water (OW), i.e. axonal and interstitial water (7, 14). Briefly, ^{1}H protons with short T_2 (e.g. those of hydration-layers and on proteins and lipids), including those near or in MW, are selectively saturated by a pair of on-resonance, T_2-selective, 10ms, adiabatic 180^0 pulses, and after a variable delay Δ the ST effect on the long-T_2 water pools is measured with a gradient echo (GRE) EPI sequence (Fig.1) with TE=40ms, which is minimally sensitive to direct contributions from MW. By analyzing the ST dependence on Δ, high specificity to MW can be achieved. High sensitivity is possible because much of the magnetization of MW is modulated due to the high prevalence of short T_2 protons, and the OW, to which most of the saturation transfers, and through which it is measured, is initially largely unsaturated and has long T_2. IRB-approved experiments were performed at 7T with TR=3s, 1.6x1.6x2mm^3 resolution, rate-2 SENSE, 5 slices with varying order after each saturation pulse (Fig. 1), Δ=9-329ms (step size 80ms), flip angle $\alpha=90^0$, 20 repetitions, 5 minute total duration. T_1 scans (to allow T_1-correction of the saturation signal) were acquired by repeating the EPI experiment with a single 180^0 pulse.

Results and Discussion: The effectiveness and selectivity of the T_2-based myelin saturation approach was confirmed by multi-component fitting of the T_2^*-weighted signal of an 80-echo GRE acquisition (7), allowing discrimination between the various water compartments in the major fiber bundles. This showed a >80% saturation of MW, a <20% saturation of OW, and an almost complete transfer of the saturation from MW to OW within 200ms, confirming earlier work (7,14). The EPI data further confirmed a delay dependent ST effect ($(M_0-S_\Delta)/M_0$, S_Δ the EPI signal at delay Δ, M_0 from scan w/o ST pulse), specific to WM, and reaching maximum at Δ=~200ms (Fig. 2; both uncorrected and T_1-corrected WM signal are shown). Images representing the fractional ST effect ($(S_9-S_\Delta)/S_9$) (Fig. 3 for Δ =169ms, no T_1 correction) showed a robust effect across subjects (n=7), strongest in WM (estimated SNR ~42, based on signal stability, or ~105 based on thermal noise only), and having an amplitude (5-12%, 7-17% after T_1 correction) in line with MW fractions derived from the multi-component fitting of the multi-echo data.

Conclusion: The novel approach presented here allows indirect mapping of brain myelin content, and may overcome some of the limitations of earlier methods that have restricted their clinical application. The proposed ST labeling introduces sensitivity to saturation transfer timing, which allows improved distinction between MW and OW, and provides an opportunity to study the kinetics of water transport between the various cellular compartments in brain tissue. The use of on-resonance saturation pulses allows efficient (low RF power) saturation, facilitating use at high field.



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