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New rapid, accurate T_2 quantification detects pathology in normal-appearing brain regions of relapsing-remitting MS patients

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ABSTRACT

Introduction: Quantitative T_2 mapping may provide an objective biomarker for occult nervous tissue pathology in relapsing-remitting multiple sclerosis (RRMS). We applied a novel echo modulation curve (EMC) algorithm to identify T_2 changes in normal-appearing brain regions of subjects with RRMS (N = 27) compared to age-matched controls (N = 38).
Methods: The EMC algorithm uses Bloch simulations to model T_2 decay curves in multi-spin-echo MRI sequences, independent of scanner, and scan-settings. T_2 values were extracted from normal-appearing white and gray matter brain regions using both expert manual regions-of-interest and user-independent FreeSurfer segmentation.
Results: Compared to conventional exponential T_2 modeling, EMC fitting provided more accurate estimations of T_2 with less variance across scans, MRI systems, and healthy individuals. Thalamic T_2 was increased 8.5% in RRMS subjects ($p < 0.001$) and could be used to discriminate RRMS from healthy controls well (AUC = 0.913). Manual segmentation detected both statistically significant increases (corpus callosum & temporal stem) and decreases (posterior limb internal capsule) in T_2 associated with RRMS diagnosis (all $p < 0.05$). In healthy controls, we also observed statistically significant T_2 differences for different white and gray matter structures.
Conclusions: The EMC algorithm precisely characterizes T_2 values, and is able to detect subtle T_2 changes in normal-appearing brain regions of RRMS patients. These presumably capture both axon and myelin changes from inflammation and neurodegeneration. Further, T_2 variations between different brain regions of healthy controls may correlate with distinct nervous tissue environments that differ from one another at a mesoscopic length-scale.

1. Introduction

Relapsing-remitting multiple sclerosis (RRMS) is a common neurological disease affecting young adults and characterized by recurrent clinically-symptomatic episodes of inflammation and the insidious progression of disability. The classic MRI hallmarks for RRMS are transient foci of contrast enhancement during acute inflammatory episodes and the gradual accumulation of T_2 or FLAIR hyperintensities. Previous studies have established that foci of T_2 prolongation correlate with inflammation, edema, demyelination, abnormal re-myelination, gliosis and/or axonal loss (Laule et al., 2011, 2013; Lund et al., 2012; MacKay et al., 2006). Although not all T_2-bright lesions are MS-related (Liu et al., 2013), the number and locations of focal T_2 hyperintensities can often help support the clinical diagnosis of MS (Polman et al., 2010). However, T_2 changes from subtle tissue pathology can be hard to detect visually on clinical MRI scans particularly during early stages of the disease. Further, visually-apparent T_2 lesions correlate poorly with patient disability or MS disease progression (Barkhof, 2002).

This radiology-pathology discordance in MS patients has been attributed to inflammation and neurodegeneration that remain occult to visible detection on conventional MRI. Several advanced techniques, such as MR spectroscopy, diffusion, and magnetization transfer MRI, have demonstrated abnormalities in normal-appearing brain regions for MS patients (Ceccarelli et al., 2007; Davie et al., 1997; Mangia et al., 2014). Subtle T_2 differences have also been observed in normal-appearing white matter as well (Bonnier et al., 2014; Laule et al., 2004). While each of these techniques may have clinical value for the

Abbreviations: AUC, area under the curve; B1+, transmit field; EMC, echo modulation curve; FLAIR, fluid-attenuated inversion recovery; SPACE, sampling perfection with application-optimized contrasts using different flip angle evolution; MPRAGE, magnetization-prepared rapid gradient-echo; SSE, single spin echo; MSE, multi-spin echo; MWF, myelin water fraction; ROI, Region of Interest; RRMS, relapsing-remitting multiple sclerosis; WM, white matter; GM, gray matter.

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early diagnosis of MS and monitoring disease progression, quantitative methods also may provide more objective markers of specific pathological components of MS. However, to realize this potential, these methods need to be accurate, stable and reproducible across different MRI protocols and imaging sites – features that remain elusive for diffusion, magnetization transfer and conventional T_2 mapping techniques.

Accurate T_2 mapping in *clinically-feasible* scan times is challenging due to the inherent bias of rapid multi spin-echo (MSE) sequences by stimulated and indirect echoes, non-rectangular slice profiles and transmit-field (B_1^+) inhomogeneities. Furthermore, this bias depends on the pulse sequence implementation and scan parameters, causing T_2 values in the same subject to vary between scanners and protocols (Deoni et al., 2003; Lebel and Wilman, 2010; Poon and Henkelman, 1992). T_2 estimation accuracy may be improved with short TR single spin echo (SSE) (Sussman et al., 2010), analytical solutions to coherence pathways in MSE acquisitions (Lebel and Wilman, 2010; Lukzen et al., 2009; Prasloski et al., 2012), model-based reconstruction approaches (Huang et al., 2012), modeling signal with non-spin echo based pulse sequences (Deoni et al., 2003; Schmitt et al., 2004; Warntjes et al., 2007), or heuristic signal model approaches (Ma et al., 2013). We have recently reported an alternative approach for accurate quantitative T_2 mapping, the echo modulation curve (EMC) algorithm, which uses a Bloch simulation to trace all coherence pathways, including all stimulated and indirect echoes during an MSE acquisition. This algorithm accounts for different slice profiles, radiofrequency pulse shapes, crusher gradients, and spin relaxation during the radiofrequency (RF) pulses (Ben-Eliezer et al., 2015a). Because the EMC algorithm incorporates the specific implementation of the MSE pulse-sequence, this method is robust to different acquisition strategies, and offers reliable mapping in clinically feasible scan times. Note that acquisitions for EMC fitting can be tailored to emphasize speed and/or accuracy for particular T_2 components. Further info can be found in a recent report including detailed analysis of T_2 mapping approaches, and demonstrating the advantage of Bloch-simulation-based approach, like EMC, over extended phase-graph (EPG) techniques (McPhee and Wilman, 2016).

Here, we used the EMC algorithm to characterize different brain regions in a cohort of clinical RRMS patients compared to healthy age-matched controls. Using this technique we were able to detect subtle, yet statistically significant, anatomy-specific T_2 differences within normal-appearing gray and white matter structures in RRMS patients. We also observed interesting T_2 differences in healthy control subjects between individual brain structures with different anatomic locations or specific functions.

2. Materials & methods

2.1. Subject enrollment & MRI protocol

This study was performed with approval from the local institutional review board. The MSE sequence was part of the routine noncontrast head protocol for patients with an established clinical diagnosis of multiple sclerosis, referred from our academic center's MS neurology specialists and scheduled on an outpatient 3-T MRI scanner with a 20-channel head & neck coil (Skyra or Prisma, Siemens Healthcare, Erlangen, Germany). MSE scan parameters were: TR = 2500 ms, Echo-spacing = 12 ms, First echo-time = 12 ms, N_{echoes} = 10, res = 1.7 × 1.7 mm^2, N_{slices} = 23, slice-thickness = 3 mm, bandwidth = 200 [Hz/Px], $T_{acquisition}$ = 2:44 min using 2× GRAPPA acceleration. The use of longer echo trains could theoretically improve T_2 fitting accuracy (Whittall et al., 1997), particularly if long T_2 components contribute to voxel signal (e.g. in more cystic MS lesions). These are not the focus of the current work and investigation of such tissues is left for future study. However, the specific absorption rate (SAR) and scan-time limitations when scanning patients in clinical settings, limited the number of echoes that could be used while keeping sufficient volumetric coverage (i.e., number of sliced). Also note that since intravenous contrast was not ordered in these subjects, the ordering clinician's suspicion for active inflammatory lesions was low. The standard MRI protocol also included sagittal 3D SPACE FLAIR, axial susceptibility-weighted imaging, and a 3D 1-mm isotropic volumetric MPRAGE sequence. A board-certified neuroradiologist confirmed typical MRI findings consistent with clinical MS (Polman et al., 2010). A board-certified neurologist reviewed the electronic medical record to confirm MS diagnosis and subtype, disease duration and the most recent documented patient-reported expanded disability scale score (PDSS) (Hohol et al., 1995). PDSS is similar, and correlates strongly, with the expanded disability status scale (EDSS) (Learmonth et al., 2013). PDSS, however, is more efficient to collect in routine clinical care. A PDSS score of "1" indicates mild disability, "2" indicates moderate disability without gait impairment, "3" reflects gait impairment without use of a cane, and "4–5" indicate early use of a cane (after 25 ft of walking) vs late use of cane (required to walk even 25 ft). During this chart review, 2 subjects with secondary progressive MS and 1 subject with primary progressive MS were identified and excluded from the study. Overall, 27 subjects with RRMS (19 females, mean age 48.5 ± 9.2 years/o) with mean disease duration of 12.6 ± 8.6 years and PDSS of 2 ± 1.8 (no units) were included in this study. A PDSS of 2 corresponds to significant problems related to MS such as visual impairment, sensory symptoms, or fatigue, but no limitations in walking ability. Age-matched control subjects (N = 38, 15 females, mean age 39.0 ± 9.6 years/o) without history of neurological disease or known white matter hyperintensities were recruited from the local community.

2.2. T_2 relaxation mapping

T_2 maps were generated via (a) pixel-by-pixel fitting of the MSE time series of DICOM images to a theoretical exponential decay of the form of $S(t) = S_0 \cdot e^{-t/T_2}$ (Levitt, 2001) and (b) using the EMC algorithm (Ben-Eliezer et al., 2015a). All fitting procedures were programmed in-house using C++ and MATLAB (The MathWorks Inc., Natick, MA). The EMC algorithm consists of an initial pre-processing stage, in which Bloch simulations of the prospective MSE protocol are performed using the exact RF pulse shapes and other parameter values used on the MRI scanner. This allows EMC to replicate the actual decay curve in MSE protocols and produce T_2 values that are independent of the particular choice of experimental parameter set. Simulations are repeated for a range of T_2 relaxation values and transmit-field (B_1^+) inhomogeneity levels (T_2 = 1 … 1000 ms, B_1^+ = 70 … 130%), producing a database of decay curves each associated with a unique [B_1^+, T_2] value pair. Once experimental MSE data are acquired, the signal time series from each pixel is matched to the simulated database of EMCs by calculating the L2 norm of the difference between the experimental and simulated decay curves, and choosing the database entry that yields the minimum norm. This minimization procedure is implemented using a full search over the entire database, which is completed in ~15 s per slice. A unique T_2 value associated with the matched EMC is then assigned to the corresponding pixel, eventually yielding the desired parametric map after the procedure is repeated for all pixels in the slice. To avoid fitting bias due to Rician noise, signal decay curves are truncated below 10% of the first time-point intensity – for both exponential and EMC fitting. This resulted in exclusion of 1–2 echoes in areas of very short T_2 values. Lastly, proton density (PD) maps are calculated by extrapolating the image from the first echo time to time t = 0 s based on the calculated T_2 map under the assumption that purely exponential decay takes place between spin excitation and the first acquisition event.

2.3. Region of Interest (ROI) analysis

Volumetric segmentation of six ROIs was performed using automated FreeSurfer software (http://surfer.nmr.mgh.harvard.edu/) based on the three-dimensional T_1-weighted MPRAGE data. The ROIs included: global white matter, cortical gray matter, thalamus, caudate nucleus,