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3 T MRI relaxometry detects T2 prolongation in the cerebral normal-appearing white matter in multiple sclerosis

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ABSTRACT

MRI at 3 T has increased sensitivity in detecting overt multiple sclerosis (MS) brain lesions; a growing body of data suggests clinically relevant damage occurs in the normal-appearing white matter (NAWM). We tested a novel pulse sequence to determine whether 3 T MRI spin–spin relaxometry detected damage in NAWM of MS patients ($n=13$) vs. age-matched normal controls [(NL) ($n=11$)]. Baseline characteristics of the MS group were: age (mean ± SD) 42.5 ± 5.4 (range 33–51 years), disease duration 9.0 ± 6.4 (range 1–22 years), Expanded Disability Status Scale score 2.5 ± 1.7 (range 1–6.5). Brain MRI measures, obtained at 3 T, included global and regional NAWM transverse relaxation rate [R2 ($=1/T2$)], derived from 3D fast spin-echo T2 prepared images, and global white matter volume fraction derived from SPGR images. The regional NAWM areas investigated were the frontal lobe, parietal lobe, and the genu and splenium of the corpus callosum. Mean NAWM R2 was lower (indicating T2 prolongation) in MS than NL in the whole brain ($p=0.00047$), frontal NAWM ($p=0.00015$), parietal NAWM ($p=0.0069$) and callosal genu ($p=0.0019$). Similarly, R2 histogram peak position was lower in NAWM in MS than NL in the whole brain ($p=0.019$). However, the normalized WM volume fractions were similar in both MS and NL ($p>0.1$). This pilot study suggests that a novel 3D fast spin-echo pulse sequence at 3 T, used to derive R2 relaxation maps, can detect tissue damage in the global and regional cerebral NAWM of MS patients that is missed by conventional lesion and atrophy measures. Such findings may represent demyelination, inflammation, glial proliferation and axonal loss.

Introduction

Magnetic resonance imaging (MRI) has played a pivotal role in the diagnosis and management of multiple sclerosis (MS) (Bakshi et al., 2008). In addition, MRI metrics have become key supportive outcome measures to explore drug efficacy in clinical trials (Bakshi et al, 2005). Conventional MRI measures have contributed to the understanding of MS pathophysiology at the macroscopic level. However, a considerable amount of evidence suggests that these measures lack specificity to underlying pathology and fail to capture diffuse occult disease affecting the cerebral white and gray matter (Neema et al., 2007a). Various advanced quantitative MRI measures have been developed that are particularly useful in revealing occult diffuse damage in the brain and spinal cord, and may therefore help resolve the dissociation between conventional MRI findings and clinical status (Neema et al., 2007b). One such technique, mapping the transverse relaxation time through T2 relaxometry, has shown promise in its ability to detect structural changes in normal-appearing white matter (NAWM) that escape detection by conventional MRI lesion measures (Neema et al., 2007a; Barbosa et al., 1994; Miller et al., 1989; Armspach et al., 1991; Grenier et al., 2002; Whittall et al., 2002).

The recent availability of high-field strength scanners, i.e. 3 T and higher, has the potential to revolutionize the research and clinical care in MS (Bakshi et al., 2008). 3 T MRI improves signal-to-noise ratio (SNR), which may enhance the sensitivity and specificity in identifying the full extent of the disease process (Schick, 2005). Such scanners reveal MS lesions in the brain with greater sensitivity than do 1.5 T scanners (Sicotte et al., 2003; Wattjes et al., 2006; Bachmann et al., 2006). T2 relaxometry at 3 T is just beginning to be applied to the

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Table 1
Demographic and clinical characteristics.

	Normal controls	Multiple sclerosis
Subjects	11	13
Men/women[a]	6/5	6/7
Age (years)[a]	42.1 ± 5.7 (33–51)	42.5 ± 5.4 (33–51)
Disease duration (years from first symptoms)	–	9.0 ± 6.4 (1–22)
Disease course:		
Relapsing-remitting	–	11
Secondary progressive	–	1
Primary progressive	–	1
Expanded Disability Status Scale score	–	2.5 ± 1.7 (1.0–6.5)
Timed 25-foot walk	–	5.1 ± 1.1 (3.8–8)
Patients on disease-modifying therapy[b]	–	7 (54%)[b]

Key: Values in table are mean ± SD (range).
[a] No significant group differences when comparing normal controls and patients.
[b] 6 patients on glatiramer acetate and 1 patient on combined glatiramer acetate and interferon.

study of the brain in MS. A recent study demonstrated myelin damage in NAWM in patients with MS using one component of the T2 relaxation curve, the short T2 component, at 3 T (Oh et al., 2007). In the present study, we used a novel pulse sequence at 3 T to determine whether MRI histogram-based T2 relaxometric analysis could detect T2 prolongation in the regional and global cerebral NAWM in patients with MS.

Methods

Subjects

Demographic and clinical characteristics of the subjects are summarized in Table 1. We identified 13 patients with MS from a consecutive sample being prospectively enrolled and monitored as part of the Comprehensive Longitudinal Investigation of MS at Brigham (CLIMB) study at the Partners MS Center, Brigham and Women's Hospital, Boston, MA. CLIMB is an ongoing prospective observational cohort study that began following patients in 2000 (Gauthier et al., 2006). Inclusion of patients with MS in the current study was based on the following criteria: 1) age 18–55; 2) baseline neurological examination, including Kurtzke Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) and Timed 25-Foot Walk (T25FW) assessment, performed by an MS specialist neurologist at the Partners MS Center; 3) established MS diagnosis at baseline of either relapsing-remitting (RR), secondary progressive or primary progressive by the International Panel criteria (Polman et al., 2005); 4) no other major medical disorder; 5) no relapse or corticosteroid use in the 4 weeks prior to study entry to avoid transient confounding effects on MRI; 6) not initiated on disease-modifying therapy in the past six months, to avoid transient confounding effects on MRI of newly started therapy. Seven of the patients (54%) were receiving disease-modifying treatment at the time of the scan (Table 1). Six patients were receiving monotherapy with glatiramer acetate, and one patient was receiving beta-interferon and glatiramer acetate in combination. Eleven normal controls with a similar distribution of age and sex to the MS patients (Table 1) with no neurological symptoms or known neurological or major medical disorders were also included. T25FW data were not available in two patients. The current study was approved by our institutional review board and all subjects gave informed consent.

MRI acquisition

All patients underwent baseline brain MRI on the same scanner using the same scanning protocol. MRI was obtained on a 3 T unit (GE Signa, General Electric Healthcare, Milwaukee, WI) using a receive-only phased array head coil. Axial brain imaging included:

1) T2-prepared (3D) images, a novel pulse sequence [(Fig. 1) (Fautz et al., 2000)]: repetition time (TR) = 1500 ms, echo time (TE) = 30 and 90 ms, slice thickness = 2 mm (76 slices — no gap), matrix = 128 × 128, zero-filled to 256 × 256, flip angle = 90°, pixel size = 0.938 × 0.938 mm, number of signal averages = 1, acquisition time = 8 min. We obtained two image sets covering the whole brain — one for each echo time. The T2 prepared sequence was originally motivated by the desire to quantify excessive brain iron in patients with MS (Bakshi et al., 2008). Because iron containing ferritin affects T2 in a way that depends on the echo spacing, we wanted to obtain spin-echo, not fast spin-echo (FSE) contrast. However, spin-echo imaging of the whole brain is slow and less sensitive than FSE, so we used an FSE readout for the acquisition but with a spin-echo preparation as described in Fautz et al. (2000). After the spin-echo preparation, the entire slice encodes were performed in a centric ordered FSE acquisition. During the next TRs, the sequence was repeated with a different echo time of the preparation. The FSE

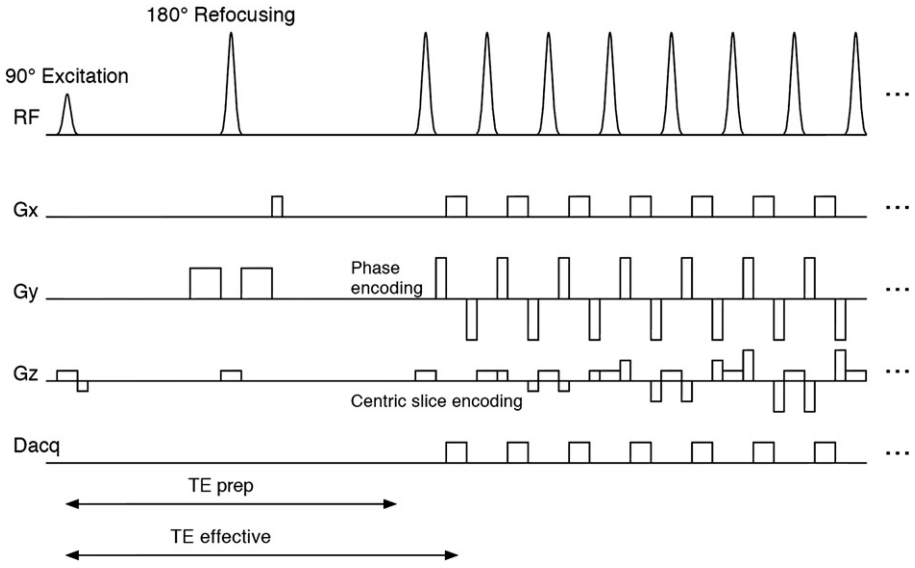

Fig. 1. Pulse sequence used for T2 relaxometry. A spin-echo preparation of duration TEprep is applied prior to a fast spin echo acquisition. The sum of TEprep and the additional time to the first data acquisition provide the effective TE of the sequence. In our acquisition, two images with different effective TE's were acquired by changing TEprep. Data was acquired with a specific phase encoding amplitude for the first effective TE and then repeated with the second effective TE. The phase encoding amplitude was then incremented and the pattern was repeated until the entire image is encoded.