Published in final edited form as:

Magn Reson Imaging. 2012 January ; 30(1): 19–25. doi:10.1016/j.mri.2011.07.018.

T1 and proton density at 7 T in patients with multiple sclerosis: an initial study

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Abstract

Magnetic resonance imaging of cortical lesions due to multiple sclerosis (MS) has been hampered by the lesions' small size and low contrast to adjacent, normal-appearing tissue. Knowing cortical lesion T1 and proton density (PD) would be highly beneficial for the process of developing and optimizing dedicated magnetic resonance (MR) sequences through computer modeling of MR tissue responses. Eight patients and seven healthy control subjects were scanned at 7 T using a series of inversion recovery turbo field echo scans with varying inversion times. Regions of interest were drawn in white matter, gray matter, cortical lesions, white matter lesions and cerebrospinal fluid. White matter and gray matter T1s were significantly higher in MS patients than in controls. Cortical and white matter lesion T1 and PD are also presented for the first time. The advantages of ultrahigh field MR imaging will be important for future investigations in MS research and sequence optimization for the detection of cortical lesions.

Keywords

Ultrahigh field; 7 T; Multiple sclerosis; Cortical lesions; White matter lesions; MRI

1. Introduction

Multiple sclerosis (MS) is one of the most common neurological disorders in young adults, affecting women more frequently than men [1]. White matter lesions (WMLs) have traditionally been the focus of MS research [2]; however, it has become increasingly clear that gray matter (GM) is also demyelinated in MS. Cortical demyelination in particular is thought to contribute significantly to the clinical deficits that accumulate during secondary progressive MS [3,4].

Histologically, cortical lesions (CLs) are classified according to their anatomical location: leukocortical lesions (type I) located on the WM/GM boundary, small intracortical lesions (type II) that are located entirely within the cortex and subpial lesions that extend from the pial surface to cortical layer 3 or 4 (type III) and oftentimes cover a large surface area, encompassing one or several gyri. Type IV lesions encompass all layers of the cortex but do not intrude into the WM [5].

Magnetic resonance imaging (MRI) of cortical demyelination in patients has proven to be difficult due to the small lesion size and low contrast to adjacent, normal-appearing tissue

[6,7]. Since conventional MRI (T2-Spin-Echo (SE), Fluid Attenuated inversion recovery (FLAIR) and pre- and postcontrast T1-weighted imaging) is not well suited for CL depiction, there have been several recent attempts and promising results at improving MRI methods for CL imaging, including double inversion recovery [4] and thin-section three-dimensional T1-weighted MRI [8]. More recently, high-resolution 7-T T2*-weighted gradient echo imaging has further improved CL detection [9–11].

Although many studies have been completed with the goal of improving CL imaging, to our knowledge, none has focused on determining the intrinsic tissue parameters that contribute to the eventual success or failure of a particular imaging method. Signal-to-noise ratio (SNR), contrast-to-noise ratio and spatial resolution optimization of these different sequences would benefit from knowledge of proton density (PD) and T1 relaxation times. The objective of this study was to produce initial CL PD and T1 measurements at 7 T in MS patients as the first step to further optimize CL detection.

2. Methods

Eight MS patients [mean age 45.3 years (range=30–58), 3 male/5 female, 5 secondary progressive MS (SPMS)/3 relapsing-remitting MS (RRMS)] and seven healthy control subjects (mean age 43.9 years [range=28–56], 3 male/4 female) were recruited and scanned at 7 T (Philips Achieva, Cleveland, OH, USA) using a 16-channel phased-array head coil (NOVA Medical, Boston, MA, USA). Informed consent and local institutional review board approval were obtained from each participant.

A series of short, inversion recovery turbo field echo (IR-TFE) scans with a shot interval of $TS=4200$ ms and inversion times of $TI=70, 200, 700, 1000, 2000$ and 2900 ms were used. Other relevant sequence parameters were as follows: repetition time (TR)=4.0 ms; echo time (TE)= 1.94 ms; flip angle=8°; TFE factor=300; acquired voxel size=0.5×0.55×1.4 mm³; reconstructed voxel size=0.23×0.23×0.70 mm³; 60 slices; total scan time=2:41 min. The short scan times were selected primarily for patient comfort and compliance. To assess any bias that may be introduced in the T1 measurements using a TI less than twice the estimated tissue T1, a second set of IR-TFE scans was acquired on three control subjects using a longer TS of 6000 ms, allowing for an additional scan with a TI of 4500 ms to be included in the series.

Lesions used in the T1 measurements were identified using additional high-SNR WM-attenuated IR-TFE and two-dimensional (2D) T2*-weighted fast field echo (FFE) scans [12]. Relevant acquisition parameters for the IR-TFE scan were as follows: $TS=3700$ ms; $TI=550$ ms; TR=4.1 ms; TE=1.6 ms; flip angle=8°; TFE factor=165; acquired voxel size=0.4×1.0×1.4 mm³; reconstructed voxel size=0.38×0.38×0.70 mm³; 128 slices; averages=2; total scan time=10:04 min. For the 2D FFE scan, relevant acquisition parameters were as follows: TR=1000 ms; TE=6.5 and 22 ms; flip angle=30°; acquired voxel size=0.33×0.33×1.0 mm³; reconstructed voxel size=0.3×0.3×1.0 mm³; 34 slices; averages=1; total scan time=8:34 min. B1 inhomogeneity is a consistent issue at ultrahigh field; thus, B1 maps were acquired for each subject, and areas with an insufficient flip angle (<50% of specified value) were excluded from analysis.

White matter lesions were identified in the high-SNR IR-TFE images as bright, focal hyperintensities within the WM regions. Cortical lesions were identified by two readers independently using structural information from the 2D FFE images [9] and GM/CL contrast from the WM-attenuated IR-TFE images (Fig. 1) using the method described in Ref. [12].

To correct for subject motion within the scan session, the IR-TFE T1 measurement scans were registered to each other using FSL (Oxford University, UK) [13,14]. Regions of interest (ROIs) for WM, GM, WMLs, CLs and cerebrospinal fluid (CSF) were drawn, and the mean signal intensities were recorded. To ensure that the same pixels were analyzed in each IR-TFE image set, the ROIs were masked onto the corresponding slices of the other five IR-TFE image sets. In the MS patients, a total of 64 ROIs were drawn in WM, 62 in GM, 22 in CLs, 23 in WMLs and 17 in CSF. In the control subjects, a total of 57 ROIs were each drawn in WM and GM, and 5 were drawn in CSF. In the long-TS scans on the control subjects, 32 ROIs were measured in WM and GM. Signal-to-noise ratio was determined in volunteer studies by repeating identical scans of both the high-SNR IR-TFE sequence and the IR-TFE T1 series. The repeated scans were subtracted, and the SNRs for selected ROIs were determined as the signal average of the two scans divided by the standard deviation of the same ROI in the subtracted image.

With the use of IDL (ITT Visual Information Systems, Boulder, CO, USA), the T1 of WM, GM, WML and CL was estimated with a nonlinear least squares curve fitting algorithm, MPFIT [15]. The algorithm iteratively fits the measured signal intensities to a theoretical relaxation curve, in this case, from the IR-TFE signal equation developed and described by Deichmann et al. [16]. Cerebrospinal fluid T1 was fitted directly using the Deichmann model for each CSF ROI and averaged. For each tissue, any T1s that exceeded this average T1_{CSF} value were excluded from further quantitative analysis. The scaling factors that were output from the curve fit algorithm were used to compute PD by normalizing them to the scaling factor of CSF, such that PD_{CSF}=1.0. As with T1, PD calculations that exceeded PD_{CSF}=1.0 were also excluded from further analysis. Welch's two-sample *t* test was implemented in the R statistical package [17] and used to analyze significance between the targeted tissues or subject groups ($\alpha=0.05$): WML/CL vs. normal-appearing WM/GM, MS vs. control and short TS vs. long TS. This particular test was chosen because it can account for the possibility that unequal variances may exist between the groups.

To test the validity of the methods presented here, the calculated T1 and PD values were included in the Deichmann et al. [16] model and plotted. The signal curves were then compared qualitatively to in vivo images.

3. Results

Fig. 1 shows example images of CLs and WMLs that were identified using the high-SNR IR-TFE and 2D FFE images. Fig. 2 shows example images of CLs and WMLs that were located using the high-SNR IR-TFE images, along with the corresponding slice in the T1 measurement data sets at TI=700 and 2000 ms. The relative increase in SNR between the high-SNR IR-TFE WM-attenuated images and the T1 measurement data was 2.8, determined by voxel and matrix size, number of averages and bandwidth. On average, the ROIs contained 38 pixels (about 2 mm² with an average radius of 0.8 mm). B1 inhomogeneity was most noticeable in the high-SNR IR-TFE images, and regions with B1 field-induced signal loss greater than 50% (Fig. 1A) were excluded from analysis.

The average calculated T1 and PD values are summarized in Table 1, and *P* values are tabulated in Table 2. Fig. 3A shows a box and a whisker plot comparing the T1 distributions of MS patients and healthy controls. Both CLs (T1=2420±610 ms) and WMLs (T1=2530±890 ms) had longer T1 than adjacent, normal-appearing WM (T1=1350±440 ms) and GM (T1=2000±580 ms), with all *P*s<.05. T1 values of normal-appearing WM and cortical GM in MS patients tended to be higher than those in healthy subjects (both *P*s<.001). The T1 relaxation times for CLs and WMLs were not statistically different from one another. In comparing the long-TS and short-TS IR-TFE series in controls, both WM

($T1_{\text{long}}=1190\pm180$ ms) and GM ($T1_{\text{long}}=2240\pm540$ ms) were significantly larger in the longer-TS scans (both $P<.001$). Since the short-TS model was insufficient for automatically fitting CSF data, the signal curves were fit manually, resulting in an average $T1_{\text{CSF}}=4470$ ms.

Fig. 3B shows the relative distributions for the calculated PDs for both MS and control subjects. The calculated PD for WMLs ($PD=0.91\pm0.13$) was larger than adjacent, normal-appearing WM ($PD=0.68\pm0.18$; $P<.001$), while CLs ($PD=0.86\pm0.17$) and normal-appearing GM ($PD=0.78\pm0.19$) were not differentiable ($P>.15$). White matter and GM PD values in MS were not statistically different to those from healthy controls (both $P>.06$), and the PDs calculated for CLs and WMLs were statistically identical ($P>.32$). Comparing the short- and long-TS/TI measurements in controls, the PDs for WM were statistically similar ($P>.13$) and those for GM were not ($P<.005$).

Fig. 4 shows that the calculated T1 and PD values were commensurate with the tissue contrast obtained in in vivo images.

4. Discussion

In healthy subjects, short IR-TFE scans with $TS/TI_{\text{max}}=4200/2900$ ms resulted in slightly shorter T1 values than previously published data [18–22]. T1 values in controls for $TS/TI_{\text{max}}=6000/4500$ ms were better matched, indicating that a longer TS is needed in future measurements, ensuring that the full relaxation curve is included in the analysis. Scan times for relaxation time measurements can be somewhat long, but methods proposed in this study require acquisitions of several image sets with a duration of less than 4 min each ($TS=6000$ ms). This was well tolerated by patients and control subjects alike.

The T1 values at 7 T for WM and GM found in literature are summarized in Table 3. Although a variety of methods are used, all the calculated T1 values are comparable to one another, including the values determined in this study. Rooney et al. [18] used a modified Look–Locker sequence with 32 samples acquired after an adiabatic excitation pulse. This resulted in a single-slice acquisition that required 23 min of scan time. This is excessive for use with patients and is not suitable for those with compromised motor control. Several authors have presented other methods for measuring tissue T1: driven equilibrium single pulse observation of T1 (DESPOT1) [21], inversion recovery echo planar imaging (IR-EPI) [19,20,22], inversion recovery turbo spin echo (IR-TSE) [19] and IR-TFE (aka magnetization prepared rapid gradient echo [MPRAGE]) [19]. The spoiled gradient echo (SPGR)-based DESPOT1 is fast and efficient for creating T1 maps, although the sequence is quite sensitive to B0 and B1 inhomogeneity, requiring significant postprocessing [21]. The IR-EPI and IR-TFE sequences resulted in very similar T1 measurements [19]. Although fast, the EPI readout is inherently low resolution and, as such, is not a good choice for measuring small anatomical structures (i.e., CLs in MS). The proposed IR-TSE sequence consistently measured lower T1 values than the other two sequences, perhaps due to magnetization transfer effects and/or imperfect modeling of the slice profile and longitudinal relaxation curves. The IR-TSE sequence also requires high SAR levels, so its application at ultrahigh field is limited.

Similar to our study, Parry et al. [23], Stevenson et al. [24] and de Graaf et al. [22] reported on the finding in MS patients in which the T1s of normal-appearing WM and GM tended to be higher than those in healthy control subjects. Our work here supports that finding as well. The increase in T1 relaxation times of normal-appearing GM and WM may be attributed to having a higher concentration of free water throughout the brain as a result of neuronal apoptosis occurring during the process of lesion formation [5,25].

Our PD results for normal-appearing WM and GM are in line with those presented by Tofts [26]. More recent PD measurements could not be found, but we expect no change of PD with increasing B0 fields. To our knowledge, CL and WML T1 and PD values have not been previously published at 7 T; thus, our results represent an important step forward in the optimization of MR sequence for detecting CLs.

While analyzing the data for WMLs, it was noted that the distribution of T1 values was distinctly bimodal. It is suggested that lesions with longer T1s may represent older, more established lesions whose high T1 values represent greater tissue damage and axonal loss [27,28]. Although beyond the scope of this study, this finding warrants further investigation.

The calculated CSF T1 is consistent with previously published results [18]. Extreme values beyond the theoretical limit imposed by the measured CSF T1 and PD were excluded from analysis. There are wide standard deviations in both the T1 and PD values of all the tissues included in this study due to significant intersubject variation. Intrasubject variation is much lower. The shorter TS used in this study may have led to shorter T1s due to some poor curve fits. Nevertheless, statistical significance was obtained for differentiating WM, GM, CL and WML in MS patients and WM and GM in control subjects. Furthermore, the precision achieved in this initial study is sufficient for our primary objective: determining WML and CL T1s and PDs to be used in contrast optimization calculations for different pulse sequences. Future studies aimed at characterization of normal-appearing tissue and lesions will require longer TS/TI_{max} and also should be controlled more tightly for ROI location and other factors including age, gender and MS treatment regimen. Such studies will also require a larger number of patients, although the data presented here can serve as a guide for these important studies.

5. Conclusion

Ultrahigh field MR provides higher tissue contrast and SNR, facilitating the measurement of the tissue parameters for CLs and WMLs. Availability of T1 and PD measurements for CLs will allow for further optimization of 7-T MRI methods and thus is a valuable step forward in expanding and improving MRI MS research.

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Fig. 1.

(A) Whole-brain high-SNR WM-attenuated IR-TFE image with the inset box indicating the anatomical area of the WM-attenuated IR-TFE (top) and T2*-weighted FFE (bottom) images. A CL (arrows) can be identified via hyperintense contrast to adjacent GM in the WM-attenuated image and by hypointense borders in the T2*-weighted FFE sequence. (B) White matter lesions are easily visible in the WM-attenuated images (arrowheads) and are also seen on the T2*-weighted FFE images. Areas of the brain with signal loss due to B1 inhomogeneity greater than 50% were excluded from the study (dotted line).

Fig. 2.

High-SNR WM-attenuated IR-TFE images showing an example of WML (A, arrowhead) and CL (B, arrow). The same lesions were identified on the T1 measurement IR-TFE images (C and D: TI=700 ms; E and F: TI=2000 ms) and used for the subsequent T1 and PD calculations. (A) and (B) have 2.8 times the image SNR than (C–F).

Fig. 3. (A) Box plot showing the relative distributions of T1 measurements for MS patients and healthy controls for WM, GM, CLs and WMLs. (B) Box plot showing the relative distributions of tissue PDs for MS patients and healthy controls.

Fig. 4.

Graph showing a representative signal response curve for an IR-TFE sequence given the calculated T1s and PDs presented in this study. White matter, GM, WMLs and CLs are included. The simulated tissue contrast is similar to that seen in in vivo images. Minimal B1 inhomogeneity can be seen in the MR images. TS=6000 ms, TR=4.0 ms, TE=1.9 ms, flip angle=8°.

Table 1
Median T1 and PD values of WM, GM, WMLs and CLs measured in MS patients

	MS patients				Controls			
	WM	WML	GM	CL	WM	GM	CL	GM
T1 (ms)	1350±440	2530±890	2000±580	2420±610	890±280	1550±530		
PD	0.68±0.18	0.91±0.13	0.78±0.19	0.86±0.17	0.63±0.18	0.71±0.20		

T1 and PD values of WM and GM of healthy controls are included for comparison.

Table 2
***P* values are shown comparing the calculated WM and GM T1 and PD for MS patients and healthy controls**

	T1 <i>P</i> value	PD <i>P</i> value
MS-WM/control-WM	<.001	NS
MS-GM/control-GM	<.001	NS
MS-WM/MS-GM	<.001	<.005
MS-WM/MS-CL	<.001	<.005
MS-WM/MS-WML	<.001	<.001
MS-GM/MS-CL	<.05	NS
MS-GM/MS-WML	<.005	<.005
MS-WML/MS-CL	NS	NS

NS: not significant.

Table 3
Summary of normal-appearing WM and GM T1 values in this study and those in recent literature

First author	Year published	WM T1 (ms)	GM T1 (ms)	Population	Method
This study	–	1350±440	2000±580	MS	IR-TFE
This study	–	890±280	1550±530	Healthy	IR-TFE
de Graaf [22]	2010	1085±100	1691±132	MS	IR-EPI
de Graaf [22]	2010	1043±45	1804±109	Healthy	IR-EPI
Wright [19]	2008	1130±100	1940±150	Healthy	IR-TFE
Wright [19]	2008	950±125	1550±125	Healthy	IR-TSE
Wright [19]	2008	1200±40	1950±125	Healthy	IR-EPI
Rooney [18]	2007	1220±36	2132±103	Healthy	Modified Look-Locker
Ikonomidou [20]	2006	1357±22	2007±45	Healthy	IR-EPI
Li [21]	2006	1500±100	2000±100	Healthy	DESPOT1