Whole Brain 3D MR Fingerprinting in Multiple Sclerosis: A Pilot Investigation

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Abstract

Background: MR fingerprinting (MRF) is a novel imaging method proposed for the diagnosis of Multiple Sclerosis (MS). This study aims to determine if MR Fingerprinting (MRF) relaxometry can differentiate frontal normal appearing white matter (F-NAWM) and splenium in patients diagnosed with MS as compared to controls and to characterize the relaxometry of demyelinating plaques relative to the time of diagnosis.

Methods: Three-dimensional (3D) MRF data were acquired on a 3.0T MRI system resulting in isotropic voxels ($1 \times 1 \times 1 \text{ mm}^3$) and a total acquisition time of 4min 38s. Data were collected on 18 subjects paired with 18 controls. Regions of interest were drawn over MRF-derived T_1 relaxometry maps encompassing selected MS lesions, F-NAWM and splenium. T_1 and T_2 relaxometry features from those segmented areas were used to classify MS lesions from F-NAWM and splenium with T-distributed stochastic neighbor embedding algorithms (T-SNE). Partial least squares discriminant analysis (PLS-DA) was performed to discriminate NAWM and Splenium in MS compared with controls.

Results: Mean out-of-fold machine learning prediction accuracy for discriminant results between MS patients and controls for F-NAWM was 65% and approached 90% for the splenium. There was significant positive correlation between time since diagnosis and MS lesions mean T_2 ($p=0.015$), minimum T_1 ($p=0.03$) and negative correlation with splenium uniformity ($p=0.04$). Perfect discrimination ($\text{AUC}=1$) was achieved between selected features from MS lesions and F-NAWM.

Conclusions: 3D-MRF has the ability to differentiate between MS and controls based on relaxometry properties from the F-NAWM and splenium. Whole brain coverage allows the assessment of quantitative properties within lesions that provide chronological assessment of the time from MS diagnosis.

Introduction

Multiple Sclerosis (MS) involves a wide spectrum of neurological symptoms resulting in challenging clinical management based on symptomatology alone (1). Magnetic Resonance Imaging (MRI) has emerged as a powerful tool in the assessment of MS (2) with the requirement that imaging is performed using standardized imaging protocols (3).

With high diagnostic sensitivity, conventional MRI is able to describe disease dissemination in time and space (4), classify MS subtypes (2) and evaluate treatment response (2, 5). However, conventional MRI may be limited when distinguishing ongoing inflammatory demyelinating pathology in normal-appearing white matter despite known disease processes (6) as well as functional disability. (7)

It has previously been demonstrated that MS pathology can be described through quantitative spatial mapping of MRI-derived relaxometry parameters, such as longitudinal (T_1) and transverse (T_2) relaxation times or proton density (PD) (8). Further, parametric mapping may overcome the aforementioned

limitations associated with MS diagnosis and staging by improving diagnostic accuracy (6, 9, 10) and predicting patient functional impairment (11, 12).

MRF is a novel MRI technique that allows quantitative mapping of T_1 , T_2 and PD using acquisition schemes followed by matching of the data to synthetically generated signals. The details of MRF have been described previously (13) and involve the repeated acquisition of image data over a time course in which acquisition parameters such as the flip angle, pulse repetition rate (TR) and echo time (TE) are intentionally modified (14). Because the resultant time evolution of the signal in a given voxel is unique for a certain combination of tissue MR properties such as PD, T_1 and T_2 , MRF derived estimates of these parameters are generated by comparing the signal evolution history of a given voxel to a dictionary of pre-simulated signal evolutions (15).

Acquiring brain relaxometry values in clinically feasible times in patients with MS have been proposed with the QRAP-MASTER pulse sequence (16). This technique has yet to meet the requirement of being obtainable within a relatively short acquisition time and as a result has had limited application as part of a standard, time constrained clinical MR examination. MRF has the potential to address this time constrain and has been described as a promising classifier of MS subtypes (17) within imaging times of several minutes. However, in that work the acquisition involved only 2D data and did not provide full brain coverage, limiting the clinical use of such an approach.

The purpose of this study is to determine if MR relaxometry maps derived from a fast 3D-MRF executed as part of a standard clinical MR examination sequence can differentiate frontal lobe normal appearing white matter (F-NAWM) and splenium in patients with MS versus healthy volunteers based solely on MRF-based relaxometry differences. Further, we hypothesize that MRF can detect MS lesions and establish a temporal relationship between relaxometry values and the time since diagnosis.

Material And Methods

Image Acquisition and Reconstruction

All clinical data were acquired on two 3T MR scanners (Discovery MR750 and Discovery MR750W, GE Healthcare, Waukesha, WI) using an eight channel receive-only RF head coil. MRF data acquisition was performed using a 3D steady state free precession (SSFP) sequence with a multi-axis spiral trajectory (18). Adiabatic inversion pulses were used before each acquisition. The flip angle ramped schedule ranged from 0.778 to 70 degrees. Sequence details can be found in (15) and (19). The acquisition FOV was $25.6 \times 25.6 \times 25.6 \text{ cm}^3$ with 1 mm isotropic voxel resolution. The total acquisition time for the whole brain volume was 4 min 38 s. The T_1 range for the dictionary was from 10 ms to 3000 ms and T_2 from 10 ms to 2000 ms. Fingerprint reconstruction and dictionary matching were performed offline using Matlab (Mathworks, Natick, Massachusetts) on a 64bit Linux workstation equipped with two 8-core Intel Xeon Gold 6244 CPU @ 3.60 GHz, 376 GB system memory, and NVIDIA Tesla V100 GPU. The reconstruction pipeline has been described elsewhere ¹⁶.

Patient population

An Institutional Review Board (IRB) approved protocol was used to obtain MRF data in patients scheduled for a clinical MR exam. Informed consent was obtained by all the participants. All methods were carried out in accordance with institutional guidelines and regulations. The MRF sequence was acquired during the clinical MRI prior to the administration of a gadolinium-based contrast agent. A total of 18 subjects with an established diagnosis of MS were included: 14 subjects had relapsing remitting MS, 3 had secondary progressive MS and 1 had primary progressive MS. Three subjects had active gadolinium enhancing MS lesions. In the control group, 18 subjects were selected and paired to age and gender for each individual with MS.

Regions of Interest Analysis

Segmentations were performed manually using 3D-Slicer software (20) as described in Fig. 1. Four to ten lesions were selected for each patient with MS, with a total of 105 lesions across 18 patients, 10 of which were active lesions. Perilesional edema was not included in the segmentation of active lesions. Additionally, for each patient, one ROI each in F-NAWM and splenium of the corpus callosum were drawn. F-NAWM was defined as areas without signal changes on the standard T2 weighted images in the clinical exam. In the control group, corresponding ROIs were drawn in the F-NAWM and splenium. First order statistics (interquartile range, skewness, uniformity, median, energy, robust mean absolute deviation, mean absolute deviation, total energy, maximum, root mean squared, 90 percentile, minimum, entropy, range, variance, 10 percentile, kurtosis, mean) obtained from each ROI were analyzed. All segmentations were reviewed by a Board certified neuroradiologist.

Statistical Analysis

Given the nature of the data, paired analysis test of statistical significance comparing regions between cases and controls was performed. Specifically, univariate comparisons were made for all individual features using non-parametric Wilcoxon signed-rank tests. Partial least squares discriminant analysis (PLS-DA) with repeated cross-validation ($n = 5$) was performed to discriminate F-NAWM and splenium in MS compared with controls, combining features from T_1 and T_2 relaxometry. Also, first order statistics features were used to classify MS lesions from F-NAWM and splenium with T-distributed stochastic neighbor embedding algorithms (T-SNE). Classification was done combining T_1 and T_2 and for each separately.

Results

Twelve of the 18 MS patients (mean age of 49 ± 13 years (mean $\pm$ SD)) were female. In the control group ($n = 18$; age mean $\pm$ SD age: 49 ± 14), 12 patients were female. Mean time since MS diagnosis was

83 months. A representative MRF-based T_1 map paired with conventional imaging weighted imaging is shown in *Fig. 2*.

Figure 3 describes the distribution of paired differences for each measurement combining T_1 and T_2 relaxometry map features. Partial least squares discriminant analysis (PLS-DA) for frontal NAWM and splenium is displayed in *Fig. 4*. Repeated cross validation ($n = 5$) showed mean out-of-fold accuracy = 65% for discriminant results between patients and controls for frontal NAWM, but mean out-of-fold accuracy approaching 90% for Splenium.

The T-SNE Plot for classification of MS lesions is displayed on *Fig. 4*. AUC analysis for selected features demonstrated that median and mean T_1 and T_2 allowed perfect discrimination ($AUC = 1$) between splenium and lesions for both T_1 and T_2 . Also, discrimination from F-NAWM was excellent ($AUC = 1$) and ($AUC = 0.98$) using median and mean for T_1 and T_2 , respectively. Table 1 lists T_1 and T_2 relaxometry ranges for all structures analyzed.

Table 1
 T_1 and T_2 mean relaxometry ranges by segment

Segment	Min T_1	Mean T_1	Max T_1	T_1 SD	Min T_2	Mean T_2	Max T_2	T_2 SD
Lesion	1071	1420	2195	259	38	75	159	25
F-NAWM (MS Patients)	738	801	885	35	27	35	45	5
Splenium (MS Patients)	720	817	980	62	24	28	35	2
F-NAWM (Control)	737	797	848	36	20	33	40	5
Splenium (Control)	683	763	831	38	13	26	34	4

Table 1: *minimum (Min), maximum (Max), mean and standard deviation (SD) along the mean values for all segmented areas. F-NAWM: frontal normal appearing white matter. All relaxometry values are in units of milliseconds.*

Table 2 lists the data used to identify if any relaxometry features were associated with time since diagnosis by all ROIs segmented. The 5 strongest rank correlations with time-since-diagnosis appear to largely correspond to T_2 mean lesion measurements as show on Table 2.

Table 2
Top 5 results are for rank correlations with time-since-diagnosis

Relaxometry	Region	Measure	Correlation	P-value
T ₂	lesion	mean	0.419	0.015
T ₁	lesion	minimum	0.367	0.033
T ₂	lesion	root mean squared	0.367	0.033
T ₁	splenium	uniformity	-0.354	0.040
T ₂	lesion	median	0.354	0.040

Table 2: *Wilcoxon rank correlation analysis. $P < 0.05$ connotes statistical significance*

Discussion

This work describes the use of a novel whole brain 3D MRF sequence (18, 21) in differentiating F-NAWM and splenium in patients with MS based on relaxometry estimates. Given the highly reproducible and accurate information provided by MR relaxometry (21, 27) the results of this study, and the isotropic whole brain coverage afforded by this technique, MRF has the potential for use in the diagnosis of patients with MS. The previously described application of MRF in the normal brain (21, 22), brain tumors (23, 24), epilepsy (25) and Parkinson disease (26), suggests that MRF has the potential for even broader application beyond MS.

MRI currently is a fundamental clinical tool when guiding therapy for patients with MS (28). Given the complexity of the condition, several studies have been conducted with more advanced MRI techniques (such as myelin water fraction or functional MRI) to predict whether MS could be diagnosed by machine learning techniques (29–32). Although the mentioned investigations have been successful, those techniques differ from MRF in that they do not provide a multi parametric approach from a single acquisition leading to lengthier exam acquisitions. Furthermore, the reproducibility of said techniques is not as well established as MRF-based relaxation estimates for both in vivo and phantom experiments (27, 33).

F-NAWM demonstrated longer relaxation in patients with MS in our study. This has been described by other quantitative imaging investigations (34). Those changes are thought to be related with myelin histological changes in the white matter poorly defined by imaging (35) and importantly could predict clinical disability (12). In this study, F-NAWM differentiation using MRF relaxation properties between cases and controls was fairly weak (mean out of fold accuracy = 65%). Given the moderate sample size, it is possible larger samples could describe more robust differentiation. Also, it is important to note prior studies (34, 36, 37) have provided estimates of the entire NAWM through the brain, potentially including areas adjacent to MS plaques that can have subtle signal changes. In order to avoid this pitfall, values

stated in this work were from segmented areas that only included white matter with no changes in the conventional T_2 weighted imaging and double inversion recovery.

Splenium is partially responsible for interhemispheric connections within the brain (38). As such, studies describing splenium changes in patients with MS (39) have focused on diffusion tensor imaging. However, histological changes in MS may also be responsible for relaxation lengthening in the splenium (34). The accuracy described in this study for classifying disease and control at this anatomical site based solely on MRF-based relaxometry changes was fairly strong (= 90%), identifying a major advantage of MRF. Given its potential to depict changes that are currently not seen or described in clinical practice, MRF may be useful, especially in those cases where the diagnosis of MS is not clearly established by more conventional well established imaging protocols.

It is known that timing since diagnosis in MS can influence normal tissue relaxation (7, 11, 37), and that those changes could predict clinical disability (40, 41). Papadoulos et al (7) described NAWM relaxation changes in a longitudinal study covering 5 years. However, Davies et al (11) found no significant differences in a three year longitudinal study after accessing T_1 quantitative changes through NAWM and GM. In this study, T_2 lengthening was observed in MS plaques on those patients with the longest time from diagnosis of MS to imaging. These findings could be related to a higher degree of Wallerian degeneration (42) although this finding has questionable clinical significance. Also, given this study was cross sectional, it would be valuable to investigate MRF through the same protocol in a longitudinal basis, so NAWM and splenium changes may be described and the faster acquisition as compared with the protocols mentioned (7, 40, 41) is a valuable tool for clinical application.

This study has several limitations. The relatively small sample size may not be sufficient to effectively establish F-NAWM and splenium changes in MS as compared to controls. Also, F-NAWM segmentations represented a minimal fraction of the overall WM in all the patients included. Both active and non-active lesions were included, as defined by gadolinium enhancement in conventional T_1 weighted imaging, but given only 10 lesions were active, this study was not powered to detect changes within relaxometry for classifying lesion activity. Future studies with larger sample sizes and volumetric segmentation through normal appearing white matter may be considered.

Conclusion

3D-MRF relaxation changes in the splenium and to a lesser degree in the F-NAWM were able to discriminate the presence of MS disease as compared to controls. Those findings corroborate the potential clinical role of MRF relaxometry where suspicious white matter changes are present, as MRF could either support or counter the presumptive diagnosis. Furthermore, quantitative evaluation of MRF derived relaxometry was helpful in characterizing the chronicity of the demyelinating lesions.

Declarations

Ethics approval: this research was ethically approved by the Mayo Clinic Institutional Review Board (IRB number: 19-004479) and all participants were consented to participate in this research. All methods were carried out in accordance with institutional guidelines and regulations.

Consent for publication: NA

Data Availability: The datasets used during the current study are available from the corresponding author on reasonable request.

Competing Interests: The authors declare that they have no competing interests.

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Figures

Figure 1

Region of Interest segmentations within MRF maps: MRF T1 relaxometry map demonstrating an active lesion in a patient with multiple sclerosis. (A) Depicts the lesion in the parietal white matter and the corresponding ROI. The T1 and T2 values and the first order statistics were simultaneously obtained from this ROI (B) shows the ROI over the frontal normal appearing white matter (2) and splenium (3).

Figure 2

Active lesion with surrounding edema in a patient confirmed with multiple sclerosis: (A) depicts the lesion in the parietal white matter on MRF-based T1 map; (B) shows the same lesion in the same clinical exam in a T1 weighted sequence, (C) illustrates the typical high intensity on a T2 weighted spin echo sequence, and (D) confirms peripheral enhancement after gadolinium injection in a T1 weighted sequence.

Figure 3

Frontal NAWM and Splenium classification for MS compared to control: Partial least squares discriminant analysis between patients (cases) and controls for splenium and frontal NAWM (normal appearing white matter) within all 18 MS patients and 18 controls.

Figure 4

T-distributed stochastic neighbor embedding clustering for all segmentations: these figures demonstrate strong clustering of the data under a T-SNE algorithm, and this allows apparently perfectly discrimination between lesions and non-lesions with T1 (A) T2 (B) and combining the two properties (C) features. NAWM: normal appearing white matter