NeuroImage: Clinical 12 (2016) 858–868

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

# Delineation of cortical pathology in multiple sclerosis using multi-surface magnetization transfer ratio imaging

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ARTICLE INFO

*Article history:*
Received 24 June 2016
Received in revised form 23 September 2016
Accepted 11 October 2016
Available online 13 October 2016

*Keywords:*
Multiple sclerosis
Sub-pial demyelination
Cortical surface
Magnetization transfer ratio
MRI

ABSTRACT

The purpose of our study was to evaluate the utility of measurements of cortical surface magnetization transfer ratio (csMTR) on the inner, mid and outer cortical boundaries as clinically accessible biomarkers of cortical gray matter pathology in multiple sclerosis (MS). Twenty-five MS patients and 12 matched controls were recruited from the MS Clinic of the Montreal Neurological Institute. Anatomical and magnetization transfer ratio (MTR) images were acquired using 3 Tesla MRI at baseline and two-year time-points. MTR maps were smoothed along meshes representing the inner, mid and outer neocortical boundaries. To evaluate csMTR reductions suggestive of sub-pial demyelination in MS patients, a mixed model analysis was carried out at both the individual vertex level and in anatomically parcellated brain regions. Our results demonstrate that focal areas of csMTR reduction are most prevalent along the outer cortical surface in the superior temporal and posterior cingulate cortices, as well as in the cuneus and precentral gyrus. Additionally, age regression analysis identified that reductions of csMTR in MS patients increase with age but appear to hit a plateau in the outer caudal anterior cingulate, as well as in the precentral and postcentral cortex. After correction for the naturally occurring gradient in cortical MTR, the difference in csMTR between the inner and outer cortex in focal areas in the brains of MS patients correlated with clinical disability. Overall, our findings support multi-surface analysis of csMTR as a sensitive marker of cortical sub-pial abnormality indicative of demyelination in MS patients.



## 1. Introduction

It is now widely recognized that standard MR imaging of multiple sclerosis (MS) can visualize only a fraction of the disease burden in cortical gray matter (cGM). In particular, conventional MRI applied at the clinically accessible MRI field strengths of 1.5 or 3 Tesla (T) cannot adequately detect the cortical gray matter pathology observed in postmortem studies, even though cGM pathology is believed to play a significant role in both cognitive dysfunction (Nielsen et al., 2013; Papadopoulou et al., 2013) and worsening clinical symptoms (Cohen-Adad et al., 2011; Nielsen et al., 2013; Mainero et al., 2015). This inability of standard MRI to visualize cortical pathology may partially contribute to the relatively weak association between MRI-visible lesions and clinical status.

A further complicating factor is that the spatial resolution and contrast of standard MRI scans at 1.5 T and 3.0 T are insufficient to detect the important sub-pial demyelination that appears to exist preferentially along the outer layer of the cortex (Peterson et al., 2001). To date, cortical sub-pial demyelination has only been visually observed *in-vivo* using ultra-high field (UHF) MRI at 7 T (Mainero et al., 2009; Cohen-Adad et al., 2011; Nielsen et al., 2012). For example, recent 7 T MRI studies employing $T_2^*$ mapping have demonstrated longer $T_2^*$ values suggestive of demyelination along the layers of the cortex in MS patients (both RRMS and SPMS) compared to controls (Mainero et al., 2015). Regrettably, UHF MRI (≥7 T imaging) is not feasible for large-scale MS clinical trials in the foreseeable future. Currently, there is only one 7 T human MRI system in Canada and approximately 50 worldwide. In contrast, over 2500 3 T systems operate globally. Since multi-center trials required for late stage drug development in MS involve hundreds of clinical sites around the world, 1.5 or 3 T systems remain the only clinically feasible options presently available. The current inability of these systems to efficiently visualize and quantify the extent of cortical pathology remains a major impediment to assessing its response to disease modifying therapies.

In this study, we address these issues using multi-surface, longitudinal measurements of magnetization transfer ratio (MTR) at the clinically-accessible MRI field strength of 3 T. MTR imaging is a semi-

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http://dx.doi.org/10.1016/j.nicl.2016.10.010

quantitative MRI technique that is sensitive to the relative degree of myelination in brain tissue (Dousset et al., 1992). It has been applied extensively in MS white matter research (Campi et al., 1996; Filippi et al., 1998; Pike et al., 1999; Rocca et al., 1999). More recently, several studies have demonstrated the utility of cortical MTR mapping for tracking demyelination in MS both *in vivo* and in post-mortem tissue samples (Schmierer et al., 2004; Chen et al., 2013; Derakhshan et al., 2014). Our previous work (Derakhshan et al., 2014) at 1.5 T, as well as the work of Samson et al. (2014), suggest subtle cortical demyelination effects can be monitored using MTR projected onto the cortical surface.

The vertex level analysis conducted in our study is supplemented by cortical surface region of interest (ROI) analysis for assessing anatomically-localized regions of the cortex where group-level, age-related decline in csMTR of MS patients exceeds that of controls. A number of previous studies have shown that age-related decline in MTR occurs in the white matter of healthy subjects (Silver et al., 1997; Schiavone et al., 2009; Newbould et al., 2014). One study identified a quadratic decrease in MTR in selected regions of cortical gray matter that occurs predominantly after 40 years of age in healthy control subjects (Mascalchi et al., 2014). To date, however, no link between sub-pial demyelination and subject age of MS patients has been found.

We test the hypothesis that the relative difference in csMTR existing between cortical surface layers in patients correlates with clinical disability in MS, as measured by the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983). Lastly, we compare csMTR values in manually segmented cortical lesions to normal-appearing gray matter (NAGM).

## 2. Materials and methods

### 2.1. Study design

Twenty-five patients with MS and 12 age and sex-matched controls were recruited from the Multiple Sclerosis Clinic of the Montreal Neurological Institute and Hospital between November 2009 and November 2010. Subject recruitment was part of a larger ongoing, longitudinal study of cortical demyelination in MS. To this end, 18 patients and 10 controls were imaged at baseline, as well as at a two-year time point to evaluate longitudinal changes in cortical MTR. Overall, the total number of examinations included in our analysis was 65.

Patient inclusion criteria were as follows: (i) subjects must have been between the ages of 20 and 70 and (ii) must have had a diagnosis of MS according to the 2005 McDonald criteria (Polman et al., 2005). Patients were not scanned within two months of a clinical relapse. All patients were on a stable treatment regime (*i.e.* they were not in the process of changing treatment and had no immediate plans to start or change treatment). There were no restrictions on the type of disease-modifying therapies used by the patients enrolled in the study. Of the 25 patient data sets analyzed, 21 had a diagnosis of relapsing-remitting MS (RRMS), while four had a diagnosis of secondary progressive MS (SPMS). The mean age of patients at baseline was 48, with ages ranging from 28 to 67. All MS patients enrolled in the study were clinically evaluated within three months of their scan date by a senior neurologist at the Multiple Sclerosis Clinic of the Montreal Neurological Institute and Hospital. At the time of evaluation, the EDSS score of each patient was determined. Written informed consent was obtained from all patients and controls; the research was approved by the Research Ethics Board of the Montreal Neurological Institute.

### 2.2. Imaging protocol

Imaging was performed on a 3 T MRI scanner (Siemens Healthcare, Erlangen, Germany) using a volume coil for radiofrequency (RF) excitation and a 12 channel coil for signal reception. Axial $T_1$-weighted images were acquired using a 3D spoiled gradient-recalled echo sequence with the following scan parameters: TR = 20 ms, TE = 5 ms, flip angle = 27 degrees, field of view = 256 × 192 × 192 $mm^3$, matrix dimensions = 256 × 192 × 192, isotropic spatial resolution of 1 $mm^3$ and total scan time = 9 min and 38 s. The $T_1$-weighted images were used for cortical surface reconstruction, cortical/white matter lesion segmentation and normalized brain volume measurements.

Four additional contrasts, also employed for lesion segmentation, were collected: Axial 2D, $T_2$-weighted images were acquired using a turbo spin-echo (TSE) sequence with TR = 4500 ms, TE = 83 ms, echo spacing = 9.18 ms, turbo factor = 11, field of view = 256 × 256 × 180 $mm^3$, matrix dimensions = 256 × 256 × 60, in-plane resolution of 1 $mm^2$, slice thickness = 3 mm, and total scan time = 3 min and 47 s; Sagittal 3D FLAIR images acquired using an inversion-prepared variable flip angle TSE sequence with TI = 2200 ms, TR = 6 s, TE = 355 ms, echo spacing = 3.3 ms, turbo factor = 141, field of view = 256 × 256 × 176 $mm^3$, matrix dimensions = 256 × 192 × 176, isotropic 1 $mm^3$ spatial resolution, GRAPPA acceleration factor R = 2 in the first phase encode direction and total scan time = 8 min and 50 s; Axial 2D, proton density weighted images were acquired using a TSE sequence with TR = 2200 ms, TE = 10 ms, echo spacing = 10.2 ms, turbo factor = 4, field of view = 256 × 256 × 180 $mm^3$, matrix dimensions = 256 × 192 × 60, in-plane resolution of 1 $mm^2$, slice thickness = 3 mm, and total scan time = 4 min and 48 s; Sagittal 3D double inversion recovery (DIR) images were acquired with a variable flip angle TSE readout, TI = 3000 ms, TR = 7.5 s, TE = 323 ms, echo spacing = 3.02 ms, turbo factor = 256, field of view = 288 × 243 × 180 $mm^3$, matrix dimensions = 256 × 192 × 176, isotropic 1.5 $mm^3$ spatial resolution, GRAPPA acceleration factor R = 2 in the first phase encode direction and total scan time = 6 min and 53 s.

Magnetization transfer ratio (MTR) maps were produced based on (i) an axial gradient echo acquisition with a Gaussian off-resonance saturation pulse +1200 Hz away from the water resonance (Sat) and (ii) a second identical acquisition without the saturation pulse (NoSat). Both the MTR sequences utilized a 3D acquisition with TR = 33 ms, TE = 3.81 ms, flip angle = 10 degrees, field of view = 256 × 192 × 192 $mm^3$, matrix dimensions = 256 × 192 × 192, isotropic 1 $mm^3$ spatial resolution, and GRAPPA acceleration factor R = 2 in the first phase encode direction. The acquisition time for each of the MTR sequences was 6 min and 34 s. To calculate MTR maps, both images were registered to the space of the $T_1$-weighted image using a hierarchical linear registration (Collins et al., 1994). At each voxel, MTR was calculated from the Sat and NoSat image intensities as 100 × (NoSat − Sat) / NoSat.

### 2.3. Image processing

Cortical surface meshes along the white matter and pial surfaces were first generated based on the $T_1$-weighted image volumes of each patient at each time point using the standard FreeSurfer analysis pipeline (Dale et al., 1999; Fischl et al., 1999a,b), version 5.1.0. All cortical surface reconstructions were visually inspected, with manual corrections applied if necessary. The FreeSurfer longitudinal analysis pipeline was then used to create unbiased, longitudinally consistent cortical surfaces for the two time points in our study. Based on the resultant white matter and pial surfaces, intermediate surfaces were generated at 25% (outer), 50% (mid) and 75% (inner) depth intervals along a Euclidean distance vector linking a vertex on the pial boundary and the white matter surface (Fig. 1) utilizing in-house developed software. To avoid partial volume contamination from cerebrospinal fluid and white matter that would occur if the pial and white matter boundaries themselves were used, the outer and inner surfaces were defined at depths of 25% and 75% respectively. Note that, in Fig. 1, the green line may not appear halfway between the red and yellow surfaces at all points because we are only looking at a particular 2D slice from a 3D volume.

To evaluate the MTR along each surface, MTR images were registered to the space of the $T_1$-weighted image and blurred along the surfaces by employing a 2D geodesic smoothing kernel with a full-width at half