Cortical Surface Analysis of Multi-contrast MR Data to Improve Detection of Cortical Pathology in Multiple Sclerosis

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Abstract. Cortical multiple sclerosis (MS) lesions are very hard to detect on magnetic resonance images, even though histopathology studies reveal that their extent can be important. Certain pulse sequences are known to help detect the lesions, but this detection is still very incomplete. To aid detection, we propose to use a cortical surface-based analysis of multi-contrast MR data in MS and healthy control subjects. We show that magnetization transfer ratio and T1-weighted scans both show differences at the group level between relapsing-remitting MS patients and healthy controls. This suggests that this approach would be useful to help detect cortical pathology in MS.

Keywords: Laminar profile, cortex, multiple sclerosis, intensity standardization.

1 Introduction

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system. Focal areas of demyelination in the white matter ("lesions") are readily apparent on conventional magnetic resonance (MR) images as hyperintense spots on T2w scans and on Gadolinium-enhanced T1w scans (in their active phase), and occasionally as hypointense spots on T1w scans (generally in their chronic phase). Subtle changes in normal-appearing white matter can also be detected by more sophisticated MR methods such as magnetization transfer ratio (MTR) [1].

MS pathology in cortical grey matter is much harder to image. Post-mortem histopathology studies have revealed that cortical involvement is present in a large fraction of patients [2] and increases as the disease progresses [3], yet cortical lesions are rarely visible on conventional MR [4,5]. The thinness of the cortex, the presence of partial voluming effects in the voxels adjacent to cerebrospinal fluid (CSF), the low myelin content of the grey matter and absent or low inflammation could all contribute to this effect [5]. Subpial lesions, which extend from the meninges into the cortex, are the most prevalent but also the hardest to see, while juxtacortical lesions, which are mixed with white matter, are the most visible [6,7]. The other types of cortical lesions (intracortical and

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whole-width) represent only 15 and 8 percent of lesions respectively [6]. While difficult to detect, cortical pathology has been linked to cognitive impairment [8], and it is therefore crucial to be able to measure its extent *in vivo*.

Particular MR sequences, including DIR, FLAIR, and high-field MP-RAGE, have been shown to facilitate detection of cortical lesions. However, comparisons with post-mortem scans show that a considerable proportion of lesions are missed by each sequence [5,9,10]. Other methods more adapted to visualizing myelin content in the brain, like myelin water fraction [11] and magnetization transfer ratio [12,13], have been applied to the cortex with some success.

In this paper, we test the hypothesis that cortical surface analysis of MR data can enhance detection of cortical anomalies in multiple sclerosis by comparing multi-contrast data in MS subjects and normal controls. Specifically, our method models the normal distributions of MR intensity features in healthy controls and uses this as a benchmark to compare MR intensity feature values in MS subjects.

2 Methods

2.1 Subjects

The data used in this paper were taken from the first time point of a longitudinal study of patients with MS conducted at the Montreal Neurological Institute and Hospital (MNI/MNH). Patients were recruited from the MS clinic at the MNH. Recruitment criteria included some degree of cognitive disability as indicated by a score of ≥ 1 on the cerebral functional system sub scale of Kurtzke's expanded disability status scale (EDSS) [14]. Patients about to start disease-modifying treatment were excluded from the study. Healthy volunteers matched for age and education level (but not gender) were recruited to serve as a healthy control group. The data used for this paper consisted of MR scans of 20 MS subjects (17 relapsing-remitting [RR], 1 primary progressive [PP] and 2 secondary progressive [SP]) and 13 healthy control (HC) subjects.

2.2 Data Acquisition

All MR data was acquired on a 3T Siemens TIM Trio scanner at the MNI. For each subject, structural T1-weighted FLASH and dual TSE T2w/PDw scans were performed (see Table 1). MTR was acquired from a PDw MT-OFF/MT-ON image pair (Siemens MT pulse: 1200Hz off-resonance, 9.984 ms duration, 100 Hz bandwidth, 500° effective pulse angle). MTR values were abnormally low in two HC subjects ($\approx$ 20% lower than in other HC subjects): data from these subjects was ignored for our analysis.

2.3 Preprocessing and Lesion in-Painting

In order to compare T1w, T2w and PDw intensities in different scans, it was important to normalize the intensities so they would be in an equivalent range.

Table 1. MR acquisition parameters

Sequence	T1w FLASH	PDw/T2w	MT-ON/OFF
Sequence	3D FLASH	dual TSE	3D FLASH
Orientation	axial	axial	axial
TR (ms)	20	2100	33
TE (ms)	5	16/80	3.81
Excitation angle	27	12	10
Slice thickness (mm)	1	3	1
In-plane resolution (mm)	1 x 1	1 x 1	1 x 1

Note that MTR does not need to be normalized as it is already a semi-quantitative measure. Most intensity standardization techniques in the literature (e.g. Nyul *et al.* [15]) rely on some form of histogram matching that makes the implicit assumption that the underlying composition of tissues in all subjects/brains is the same (so that white matter in all brains should have the same intensity and an equivalent volume, for example). Because in MS the pathology is known to affect properties of the brain tissue even in areas where there are no lesions (so-called normal appearing white/grey matter), such an assumption cannot be made and these methods are inadequate for our purposes. We therefore used non-brain tissue (defined as all tissue visible on the MR scan with the exception of the brain; that is, muscle, bone, fat, skin) to perform intensity scaling, based on the assumption that MS should not significantly affect the composition of these tissues. This standardization was performed after non-uniformity correction using N3 [16]. T1w intensities were linearly rescaled so that the 0.5th percentile and 99.5th percentile of the non-brain tissue intensities were re-mapped to 1 and to 1000 respectively on an arbitrary standard scale. Because both T2w and PDw non-brain tissue intensity histogram had a distinct peak at low intensities, we used this feature for intensity standardization between scans. The intensities were linearly rescaled on both the T2w and PDw scans so that the non-brain low-intensity peak was re-mapped to 500 while the 99.5th non-brain intensity percentile was mapped to 1000.

Because MS lesions in the white matter are often hypointense on T1w images, voxels in white matter lesions adjacent to grey matter structures may be mistaken for grey matter voxels by classification algorithms, which can seriously decrease the quality of a subsequent cortical extraction. To reduce occurrences of this problem, the intensity of voxels in white matter lesions were artificially corrected to match more closely that of the surrounding normal white matter voxels. Lesions masks were defined automatically on the T2w image, and then manually corrected. The T2w lesion masks were resampled to the T1w image space after linear registration of the T1w and T2w images, and the masks were dilated once. An implementation of the in-painting method developed by Criminisi *et al.* [17] was used to in-paint the areas defined by the lesion mask on the T1w volume; this method has the advantage of retaining borders quite well, which is important to maintain the boundary between white and grey matter intact as much as possible.

2.4 Cortical Extraction

Pre-processed T1-weighted images were used for cortical extraction. In pre-processing, the images were corrected for non-uniformity using N3 [16], denoised using a non-local means method [18] and lesion in-painted. The FreeSurfer cortical extraction pipeline [19] was run on all subjects. Manual corrections were made at intermediate steps of the cortical extraction as needed (e.g. adjusting the threshold of the initial brain segmentation or manually editing erroneous brain masks). The cortical extraction failed in three subjects (2 RRMS, 1 PPMS): these data were not included in further analysis.

After cortical extraction, each cortical surface was registered to a common template (fsaverage) based on surface curvature pattern as part of the FreeSurfer pipeline [20]. In order to have the same number of vertices in all subjects, we performed an extra registration step in which each point on the spherical template surface was associated with its closest point on the spherical registered subject surface. In this way we obtained for each subject the correspondence between vertices on the native surfaces and on the template surface. This correspondence was used later in our analysis.

2.5 Cortical Post-Processing

Cortical profiles were created by extending a straight line from each outer surface vertex to the corresponding inner vertex surface (where correspondence was intrinsically known from the FreeSurfer cortical extraction process). Twenty-one equally spaced points were created along each profile, with point coordinates interpolated from the coordinates of the outer and inner surface vertices. This number was chosen arbitrarily to allow flexibility in the definitions of features, as it allows us to separate the cortical thickness into a two, four, five or ten sections. The cortical thickness at each point was defined as the real-space distance between these vertices.

2.6 Features

Nine features were defined at each vertex of the cortical surfaces. These included cortical thickness and two features per contrast (MTR, T1w, T2w, PDw). A value of each contrast was estimated at all profile points (21 per vertex) by linear interpolation on the raw MTR data and after non-uniformity correction and intensity standardization (but not lesion in-painting) for T1w, T2w and PDw data. These values were smoothed along the cortical surface with a smoothing kernel of size 5 (FWHM, in mesh units) using the SurfStatSmooth tool of the SurfStat Toolbox [21] to reduce the noise. Blurring along the cortical surface gives an important advantage over blurring in the 3D volumetric data, as it is possible to blur across the grey matter, white matter and CSF voxels in the latter while blurring is constrained to the cortical grey matter in the former.

The features were defined as the intensity at mid-cortical depth, and the ratio between the intensity in the inner half and outer half of the cortical thickness

Table 2. Feature definitions

Feature	Definition
1	Cortical thickness (mm)
2	MTR at mid-cortical surface
3	ratio of inner to outer MTR
4	T1w intensity at mid-cortical surface
5	ratio of inner to outer T1w intensity
6	T2w intensity at mid-cortical surface
7	ratio of inner to outer T2w intensity
8	PDw intensity at mid-cortical surface
9	ratio of inner to outer PDw intensity

(see Table 2. These features were selected for their predicted sensitivity to subpial, mixed grey-white matter, and whole-cortical width lesions.

2.7 Normal Model

Using the set of correspondence between each cortical surface and the template surface (see Section 2.4), features from all subjects were mapped onto a common template surface. The values were smoothed along the template surface using the SurfStatSmooth tool with a kernel size of 8 (FWHM, in mesh units). For each vertex, a model of normal feature value distribution was established by fitting a Gaussian to the distribution of feature values in that vertex across all healthy control subjects. While the distribution of these feature values is not perfectly Gaussian, this representation was deemed adequate for this study. This yielded a very compact description of the model, as it was completely defined by the values of μ and σ at each vertex of the template surface facilitating comparison of the MS patient data to the normal model. After mapping into the common surface space as described above, the MS patient data can be compared in a vertex-to-vertex fashion to obtain a local z-score. In addition, to verify the model, each healthy control subject was compared to a model of normal feature distribution based on all other healthy control subjects in a leave-one-out fashion.

2.8 Visualization on MR

The results of the surface-based analysis were finally mapped back to the original MR volumes to allow visualization of the feature (or z-score) values simultaneously with the MR data. The feature values at each vertex of the surfaces were propagated to all voxels that the profile crosses.

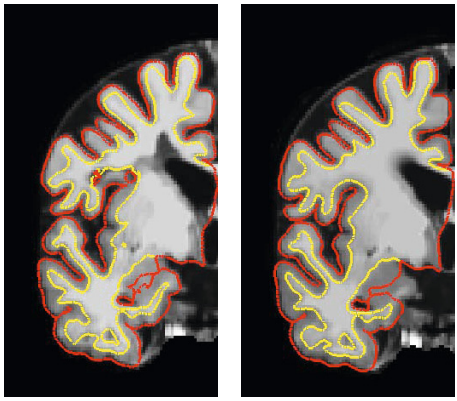
3 Results

The effects of lesion in-painting are shown in Figure 1. Most lesions are effectively removed, with the exception of very large lesions that sometimes retain a core of low intensity values, but this almost always occurs well away from the cortical surface.

Intensity standardization made the intensities of T1w, PD2w and T2w images much more similar (see Figures 2). The bounds used for re-scaling (percentile values and peak locations) were not significantly different in the HC and MS groups (see Table 3), suggesting that these are good reference intensities since they appear to be independent of disease status.

Figure 3 shows cortical thickness in mm as a z-score for two subjects (one HC and one RR). Figure 4 shows the averaged z-score of all the HC subjects, all the RR subjects and all the SP subjects. Qualitatively, we find that on average,

- cortical thickness is lower in RR, and much lower in SP MS subjects;
- MTR at midsurface is lower in RR and SP MS subjects;
- the ratio of inner to outer cortical MTR is higher in RR and SP MS subjects;
- T1w intensity at midsurface is slightly lower in RR, and much lower in SP MS subjects;
- the ratio of inner to outer cortical T1w intensity is higher in RR, and much higher in SP MS subjects;
- T2w intensity at midsurface is lower in RR, and more extreme (high and low) in SP MS subjects;
- the ratio of inner to outer cortical T2w intensity is higher in SP;
- PDw intensity at midsurface is lower in RR and much lower in SP MS subjects.



(a) (b)

Fig. 1. Outer (*red*) and inner (*yellow*) cortical surfaces resulting from cortical extraction on original T1w image (a) and lesion-inpainted T1w image (b)

4 Discussion

Our results are in agreement with previously published reports of decreased cortical thickness [22], decreased cortical MTR [12,23]; increased ratio of inner to outer cortical MTR [24]; and decreased cortical T1w intensity [25].

Table 3. Reference intensity values used for intensity standardization (mean ± standard deviation)

Contrast	HC subjects		MS subjects	
	low	high	low	high
T1w	2.3 ± 0.6	380 ± 60	2.4 ± 0.6	390 ± 40
T2w	240 ± 30	1190 ± 80	240 ± 40	1230 ± 140
PDw	810 ± 130	1800 ± 200	810 ± 180	1870 ± 80

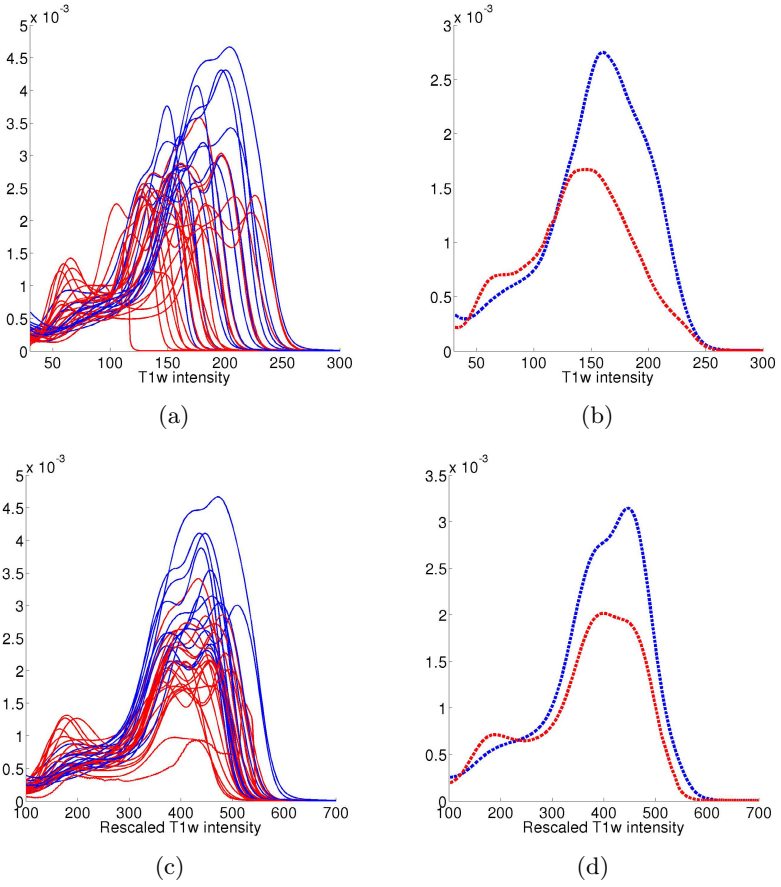


Fig. 2. Histograms of brain (excluding lesions) T1w intensity values for MS subjects (*red*) and HC subjects (*blue*) before (a) and after (c) intensity standardization, and corresponding cumulative histograms (b,d) for all MS (*red*) and all HC (*blue*) subjects

A recent post-mortem study by Tardif *et al.* [26] found increased T1 values in subpial lesions compared to normal-appearing cortex, which is consistent with our observation of higher T1w inner-to-outer intensity ratio in MS subjects. Subpial lesions would cause a decrease in T1w intensity along the outer cortical

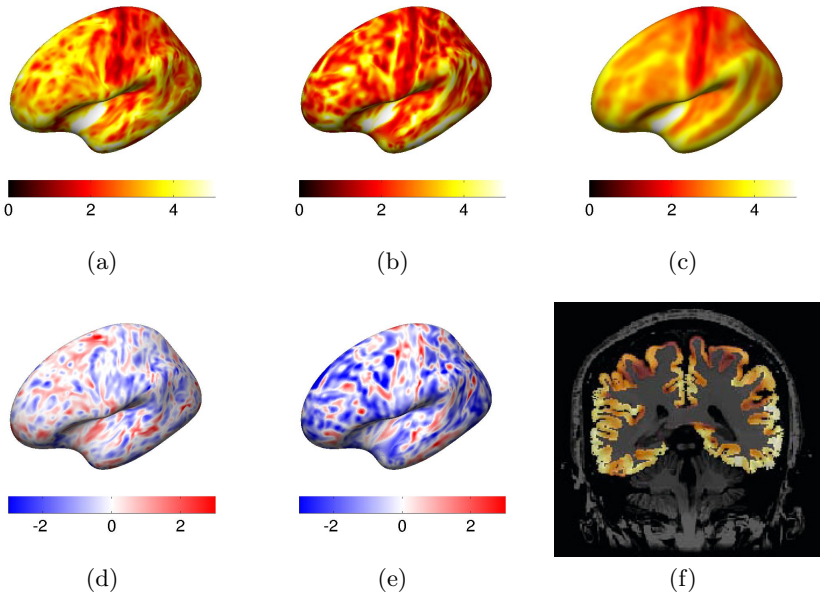


Fig. 3. Example results displayed on inflated template surface (left hemisphere only). Cortical thickness in one HC subject (a) and in one RR MS subject (b); model mean cortical thickness (c); z-score of cortical thickness in same HC subject (d) and RR MS subject (e); overlay of cortical thickness on MR volume (T1w) in same HC subject (f).

surface (as T1 values are known to correlate with myelin content in the cortex [27]).

We find that T2w intensity is lower in RR subjects, while in SP subjects, the T2w intensity was higher in some regions but lower in other (this was a pattern present in both subjects rather than an artefact of averaging) and the ratio of inner to outer cortical T2w intensity was higher. According to Tardif *et al.* [26], the T2 values of cortical lesions are higher than those of normal-appearing cortex, which should result in higher T2w midcortical intensities. The higher ratio of inner to outer cortical T2w intensities could result from T2 increases in mixed grey-white lesions, or might be the result of partial volume effects with CSF in the outer cortical layers. This hypothesis will be tested in future work by evaluating the correlation between cortical thickness and T2w intensity.

Finally, we find that PDw intensity was reduced in MS subjects, in contrast to white matter PDw intensity which is known to be higher in white matter lesions. This could be due to a lack of edema/inflammation in the grey matter combined with neuronal loss, though partial volume effects with CSF could also be at play.

The model presented here is observer independent and therefore provides an unbiased description of changes in the cortical grey matter, as opposed to lesion counts, for example, which might vary across observers. This model also combines

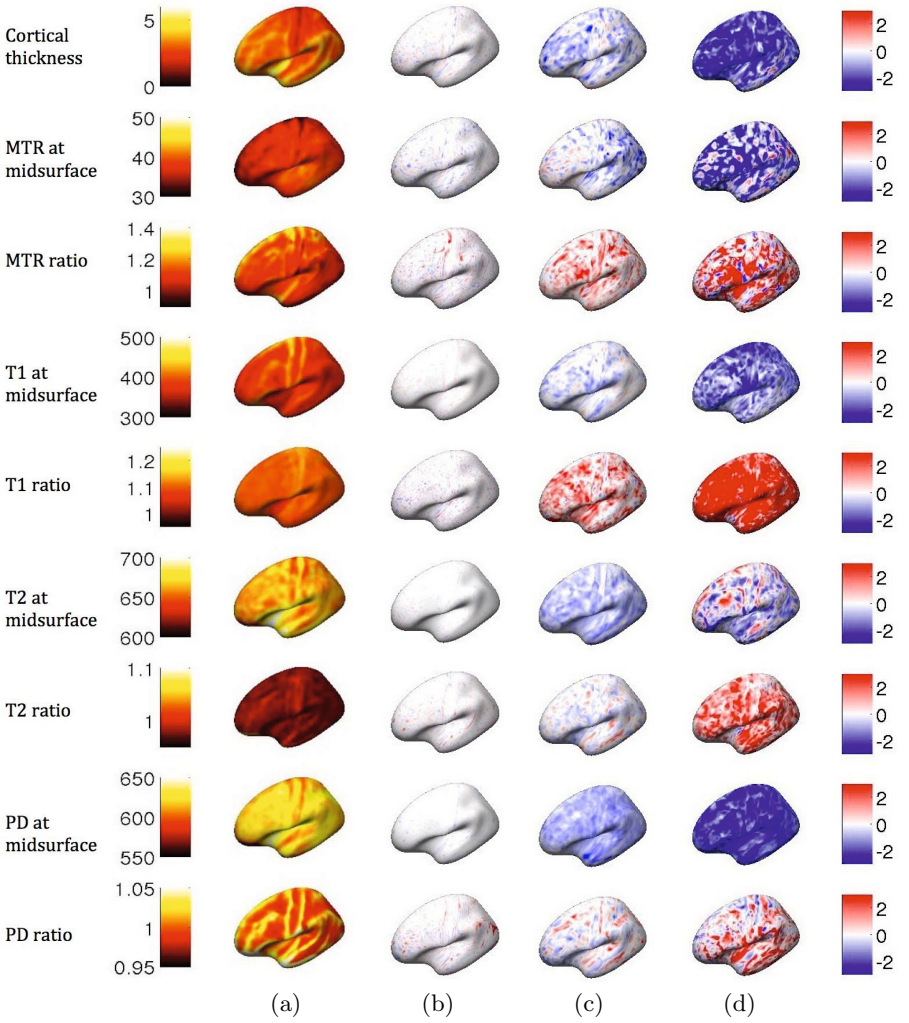


Fig. 4. Group averages displayed on inflated template surface (left hemisphere only). Model mean feature value (a), mean z-scores of 11 HC subjects (b), 16 RR subjects (c), and 2 SP subjects (d).

information from multiple contrasts as well as cortical thickness, which should make it more sensitive to cortical pathology than methods that rely on any single measurement/contrast (e.g. cortical thickness, MTR, DIR). Moreover, by considering local feature behaviour along the cortical surface, we eliminate some of the anatomically dependent variation in MR contrast intensities and patterns, though this introduces some dependence on the quality of the surface registration to the template surface.

This method is sensitive to failures of the cortical extraction, as failure to include abnormal cortical tissue (for example, because in subpial lesions, the decreased T1w intensity values at the outer edge of the cortex could shift the detected pial surface inward) would skew our results. A failure of this kind would be difficult to detect by visual inspection of the cortical surface on MRI images, since subpial lesions can be thin and quite extensive and therefore the effect on the cortical extraction would be subtle. Extending all cortical profiles outwards towards the CSF would provide confidence that the entire cortex is included, and could allow detection of subtle differences between low-T1w-intensity cortex and CSF. Similarly, extending cortical profiles towards the white matter would help insure that no mixed white-grey matter lesions are missed.

A specific and sensitive method of detection of cortical disease *in vivo* is essential to study progression and pathology of cortical disease, and this paper presents a novel method to detect cortical lesions and anomalies in multiple sclerosis. We plan to extend this work (1) to consider individual subject classification based on cortical MR features; (2) to evaluate the relationship between cortical features and manually labeled cortical lesions visible on DIR; and (3) to look for correlations of these features with gender and with cognitive impairment. Finally, a better validation will involve applying this technique to post-mortem data for which some histopathology results are available.

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