Segmentation of a Novel Lesion Type from MTR Images For Multiple Sclerosis Clinical Trials

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Introduction

Magnetic resonance (MR) imaging has revolutionized the diagnosis and treatment of multiple sclerosis (MS) and other demyelinating diseases of the central nervous system. MR is used both to detect[1] the disease and has a role as a surrogate marker in assessing the efficacy of new treatments[2]. Typically, the volume of hyperintense lesions on T2-weighted scans (T2 lesions) is used as a measure of accumulated disease burden. Enhancing lesions on T1-weighted scans with a gadolinium contrast agent (Gd lesions) indicate areas of blood-brain barrier impairment, where inflammatory demyelination is actively occurring. The number of Gd lesions is used as an indicator of acute disease activity. MR metrics are easy to quantify and analyze and are very sensitive, potentially allowing smaller clinical trials. However, conventional MR metrics have a modest correlation with clinical measures such as relapses and disability[2], limiting their use as primary endpoints in pivotal trials. T2 hyperintensity is notoriously nonspecific, and T2-weighted imaging cannot adequately measure remyelination, an important repair process in MS. Gadolinium enhancement also does not inform regarding myelin content, and the lifetime of a Gd lesion is brief, causing many to be missed on low-frequency serial imaging[3]. Thus, many subjects will not have any Gd lesions on a given scan, particularly if effectively treated. This eliminates some of the sample size benefits of MR imaging, especially in head-to-head trials. Additionally, promising techniques to measure demyelination and remyelination within MS lesions using magnetization transfer ratio (MTR) or myelin water fraction (MWF) imaging may be frustrated by high lesion heterogeneity due to the non-specificity of Gd and T2 lesions[4].

We propose that metrics based on lesions identified from myelin-specific imaging, specifically longitudinal changes in MTR, may be an important supplement to those based on Gd and T2 lesions, and a more appropriate basis for longitudinal demyelination and remyelination measurements. Here we present a simple method for identifying such lesions automatically.

Methods

Imaging data from a group of 15 adult subjects with relapsing remitting MS (RRMS) was collected. This data included standard T1-, T2-, PD- and Gd enhanced T1-weighted anatomical imaging and MTR acquisitions from at least three timepoints. As the data were acquired on different scanners, the MTR images were normalized[5]. Gray matter (GM), white matter (WM), cerebrospinal fluid (CSF) and T2 lesion masks were produced from the anatomical imaging using a Bayesian classifier. The T2 lesion masks were corrected, and Gd lesions segmented manually, by trained readers. Although Gd lesions as small as three voxels were identified, for the present work, the resulting masks were filtered to eliminate any lesions smaller than five voxels.

In order to identify lesions exhibiting *new* activity, maps of the difference between MTR images acquired at two timepoints were produced. These ΔMTR images are analogous to T2 subtraction images[3]. Voxels exhibiting greater than normal decrease in MTR intensity were identified according to modified criteria suggested by Chen *et. al.*[4]: the voxel must (a) be identified as brain tissue at both timepoints, (b) have an MTR value greater than the 75th percentile of GM voxels at the first timepoint and (c) show a greater decrease in MTR than the 1st percentile of high confidence WM voxels. Criteria (a) and (b) disqualify voxels that are not brain tissue or suffer from partial volume effect at one or both timepoints, reducing false positives from registration errors; (c) ensures only voxels with an MTR change greater than that expected from noise are included. "ΔMTR lesions" were then identified through a region growing process that requires that (d) at least one candidate lesion voxel is also identified as part of a T2 lesion and (e) the lesion has at least a minimal volume (5 voxels was used for this study). Criterion (d) reduces false positives due to image artifacts, especially motion artifacts.

To evaluate the statistical power of remyelination measurements in each of Gd and ΔMTR lesions, a simple remyelination metric was calculated; the "MTR drop" is the difference in MTR signal within a lesion between measurements taken before the lesion formed and measurements taken after the tissue had an opportunity to remyelinate. A larger decrease in signal between these two timepoints indicates more unrepaired myelin loss in the lesion. Means and standard deviations for this metric were calculated and sample size calculations performed for a simple *t*-test. Additionally, the number of subjects with analyzable lesions of each type was calculated, and these values were used to adjust the sample size to indicate the number of subjects that would need to be enrolled in a trial.

Results

Figure 1 shows an example slice from one of the subjects. (A) and (B) are MTR images from successive timepoints. Two lesions which are apparent on (B) but not (A) are indicated (blue arrows). (C) is a ΔMTR image showing the lesions as areas of decreased MTR and (D) shows a zoomed version of one lesion, with the segmented ΔMTR lesion indicated by a contour. Sample size requirements for the MTR drop metric are provided in the table.

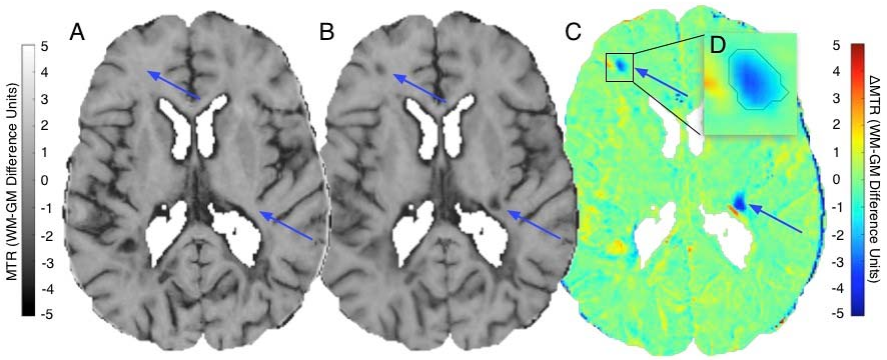

Figure 1: MTR images from two timepoints (A and B), a ΔMTR image (C) and inset showing a segmented ΔMTR lesion (D, contour line). New lesions appearing between A and B are marked with blue arrows.

Conclusion

Mean MTR drop values were similar in Gd and ΔMTR lesions, producing similar raw sample size requirements. However, more subjects had at least one ΔMTR lesion than had Gd lesions. Since subjects with no lesions are lost to analysis, a real trial would have to allow for this attrition, and a ΔMTR lesion based trial would require fewer subjects. The increased prevalence of ΔMTR lesions, as well as their greater theoretical specificity for myelin, suggest that ΔMTR lesions may be a useful and statistically powerful complement to existing T2 and Gd based techniques, particularly for the assessment of remyelinating therapies.

Table 1: Required sample sizes to detect a treatment effect of 25% on MTR drop (α=0.05, β=0.8), and lesion prevalence for Gd and ΔMTR lesions

Lesion Type	Required N	Subjects with Lesions	Trial Enrollment
Gd	28	53%	53
ΔMTR	26	73%	36

References

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