Normalization of Magnetization Transfer Ratio MRI For Multicentre Clinical Trials

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Introduction

Magnetization transfer ratio (MTR) magnetic resonance (MR) imaging is a promising technique for measuring *in vivo* demyelination and remyelination, providing a more direct measurement of activity in diseases like multiple sclerosis (MS).[1] Incorporation of MTR in multicentre imaging protocols is feasible using stock sequences and MT pulses.[2] However, such MTR values are sequence and scanner-dependent. Standardized protocols[3] that minimize MTR differences across scanners require a level of control over the MT pulse characteristics that is unavailable in large, multicentre studies. In addition, significant shifts in MTR contrast have been observed in individual scanners after upgrades. Therefore, multicentre and longitudinal studies would benefit from MTR normalization to map raw MTR data onto a common scale. If this scale is semi-quantitative, comparison to published data becomes possible.

Normalization to an external standard is cumbersome and depends upon the stability of the standard. Using an internal standard in studies of patients with diseases such as MS which may have substantial diffuse pathology is not ideal, as numerous studies have shown that normal-appearing tissues in MS exhibit abnormal MTR[2], and often it is these changes that are of particular interest.

A method to account for centre-to-centre variance in MTR images as an integrated part of the analysis process has recently been proposed.[4] In this method, MTR data from various centres is analyzed using a statistical model that includes the centre as a factor, in addition to any factors of interest, such as treatment vs. placebo.

We currently propose a method to normalize MTR images directly using a reference scan of a normal subject acquired at each site.

Methods

Five MS patients and one control were scanned at each of Site 1 and Site 2. Additionally, all the patients scanned at Site 2 were subsequently scanned at least once at Site 1. For all subjects at all timepoints, gray matter (GM) and white matter (WM) probability maps were calculated. For each centre's control subject, median MTR values were calculated for the > 85% probability GM ($GM_{MTR\text{-}C}$) and WM ($WM_{MTR\text{-}C}$). MTR data acquired at each site was normalized according to $MTR_{norm} = \frac{MTR_{raw} - GM_{MTR-C}}{(WM_{MTR-C} - GM_{MTR-C})}$.

The proposed normalization technique and a statistical model based technique were compared to determine the sample size required to see a hypothetical change equal to 10% of the normal WM-GM difference. Median raw and normalized MTR values were calculated for each patient at baseline from the > 85% probability normal appearing WM. A hypothetical second timepoint was constructed with the same variance but with a 10% decrease in the WM. The normalized WM MTR was analyzed using a general linear model (GLM) with timepoint as a factor and the raw MTR data with both timepoint and site as factors. The minimum sample size for each method to detect the change with $\alpha = 0.05$ and $\beta = 0.2$ was calculated.

Results

Median WM and GM timecourses showed greatly reduced variability after normalization (Figure 1) for patients scanned at both sites. Sample size to detect a 10% change in WM MTR was estimated to be 19 for the proposed normalization method and 18 for the statistical method.

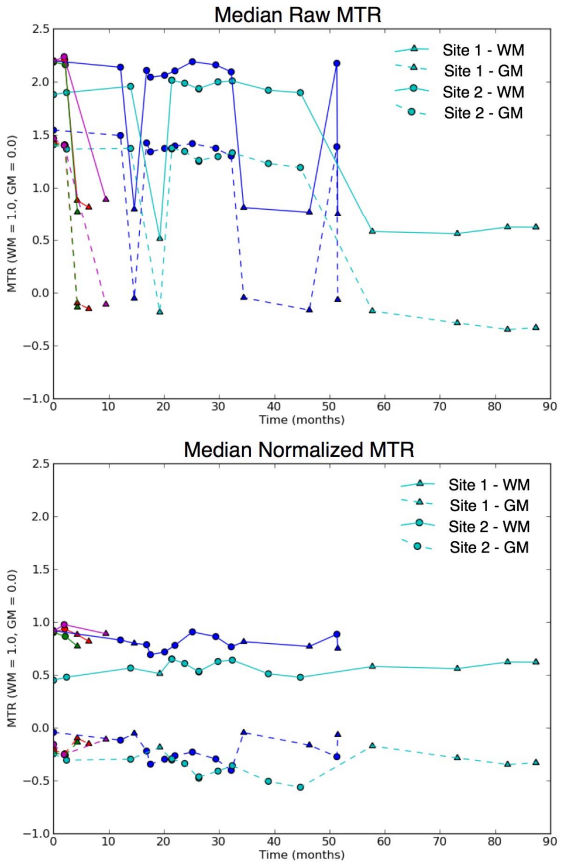

Figure 1: Median WM and GM MTR timecourses for subjects scanned alternately at both sites, before and after normalization.

Conclusions

The proposed normalization method effectively removed site-to-site variability in MTR (Figure 1). Both our proposed method and the statistical modeling approach were able to achieve high statistical power with multicentre data. Although the statistical approach does not require control data for normalization, it assumes that subject selection across sites is homogeneous and requires a reasonable sample size at each site. Our proposed method produces semi-quantitative MTR maps that may be compared across studies, and facilitates more sophisticated analyses of the dynamics of focal and regional MTR change over time.

Reference

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