Prediction of disease course in multiple sclerosis using cortical thinning measurements at baseline

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Introduction:

The ability to predict the disease course in Multiple Sclerosis (MS) would greatly help in the individual patient management. Published reports suggest that cortical pathology appears early on in the disease. In this study, we evaluated if cortical thickness is useful in predicting the disease course in a large cohort of relapsing remitting MS (RRMS) patients who participated in a multi-center phase 3 clinical trial (CombiRx). Cortical thickness was measured using high resolution 3D T1-weighted MRI at baseline and 6 months and correlated with extended disability status scale (EDSS) at 36 months. Our results indicate that significant cortical thinning in some cortical structures at baseline (before treatment) that does not improve at 6 months (following treatment) predicts the clinical status at 36 months.

Methods:

Five hundred and ninety six (437 females) RRMS patients with average age of 38.15 (± 11.10; range: 18-60) years from the CombiRx clinical trial were included in this study. These patients underwent MRI sequences per protocol at five time points, baseline, 6, 12, 24, and 36 months. EDSS was recorded at every three months from baseline (0 month) to 36 months. Median EDSS at baseline was 2 (range: 0-6.0). Additionally, 400 (298 females) healthy controls with mean age of 37.68 (± 10.93; range: 20-61) years were included. MR protocol for MS patients included two-dimensional (2D) dual fast spin echo (FSE), fluid attenuated inversion recovery (FLAIR), pre- and post-contrast T1-weighted, and 3D T1-weighted images. Images were pre-processed for skull-stripping, bias field correction and 2D images were co-aligned with 3D images using affine transformation[1-3]. Lesions, WM, GM, and CSF were segmented in MS brains using 2D FSE and FLAIR images using unified non-parametric and parametric technique which were then co-aligned with the 3D T1-weighted images using affine transformation matrix[4]. 3D T1-weighted images of MS patients were in-painted for lesions[5]. FreeSurfer was applied to 3D in-painted T1-weighted images to determine cortical thickness in 68 structures (34 each in left and right hemisphere)[6-8].

Generalized linear regression model was applied to assess the effects of age and gender on cortical thickness values in the control group. Significant effects were observed and therefore cortical thickness values were corrected for age and gender using regression coefficients. The cortical thickness values for each structure in MS patients were corrected for age and gender using regression coefficients derived from control data. Normative data from the controls was obtained by computing the z-scores using mean and standard deviations for each structure. The z-scores for each structure for the MS patients were calculated using the mean and standard deviations obtained from control group[9]. Significant cortical thinning in MS patients was automatically detected using a threshold on the z-scores ($|z| > 3.37$) at p-value of 0.05 with Bonferroni correction. Structures with significant cortical thinning (cortical thickness z-scores values less than critical threshold, $z < -3.37$) at baseline were analyzed for predicting the disease status at 36 months.

Results:

A total of 1810 structures (pooled from all patients) showed significant cortical thinning as measured by cortical thickness z-scores values (< -3.37) at baseline. The correlation between these z-scores and the EDSS at 36 months was found to be 0.136 ($p < 0.0001$). We further divided these structures into two groups, group I consisting of the structures (573) that have significant cortical thinning at baseline and 6 months, and group II consisting of structures (1237) that showed significant cortical thinning only at baseline, but with z-scores within normative range at 6 months. The z-scores of group I structures significantly correlated with EDSS at 36 months ($R = 0.299$, p-value < 0.0001) (figure 1A) but the z-scores of group II structures did not correlate with EDSS at 36 months. This analysis was also performed for individual structures from group I. Of all the structures, significant correlations were observed for inferior parietal gyrus ($R = 0.797$, p-value < 0.001), temporal pole ($R = 0.691$, p-value = 0.018), and supramarginal gyrus ($R = 0.598$, p-value = 0.003), all in the right

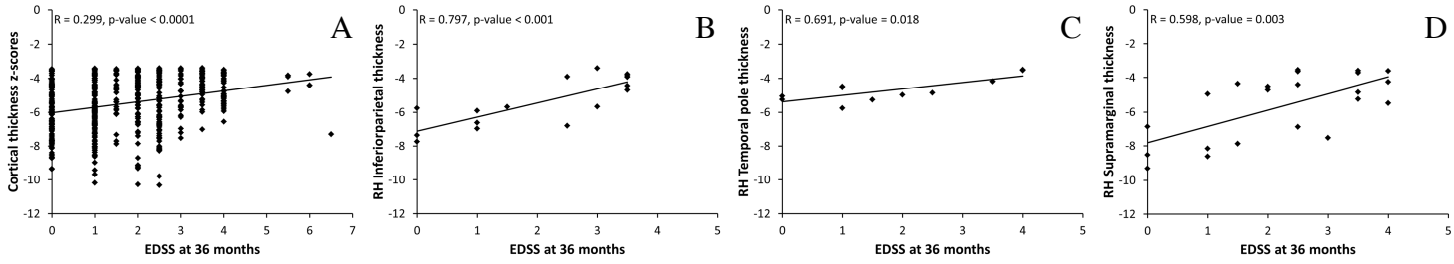

Figure 1. Scatter plots of cortical thickness z-scores at 0 month vs EDSS at 36-months. (A) All structures from all patients with z-scores < -3.37 at both 0 and 6 months (group I); (B) inferior parietal thickness from 16 patients that had z-scores < -3.37 at both baseline and 6 months; (C) Temporal pole thickness from 22 patients that had z-scores <-3.37 at both baseline and 6 months; and (D) supramarginal thickness from 11 patients that had z-scores < -3.37 at both baseline and 6 months.

hemisphere (figures 1B-1D).

Discussion and Conclusions:

We have analyzed the cortical thickness of various structures in MS at baseline and 6 months by creating a range of normative thickness values from healthy controls and identifying the structures in MS patients with significant thinning using the deviation from normative data. Our results indicate that significant cortical thinning of the structures at both baseline and 6 months can predict the disease status at 36 months in MS. Analysis based on individual cortical structures indicates that the cortical thinning of inferior parietal gyrus, temporal pole, and supramarginal gyrus in right hemisphere at both baseline and 6 months can predict the disease course in individual MS patients, as indicated by the high R values.

References: **[1]** Smith, HBM 2002;17:143-155, **[2]** Tustison et al., IEEE TMI 2010;29:1310-1320, **[3]** Avants et al., MIA 2008;12:26-41, **[4]** Sajja et al., ABE 2006;34:142-151, **[5]** Datta et al., Proc. of ISMRM 2014, **[6]** Dale et al., N 1999;9:179:194, **[7]** Fischl et al., N 1999;9:195:207, **[8]** Narayana et al., NC 2013; 2:184-96, **[9]** Bouix et al., PLoS One. 2013;8:e6605.