

# Morphogenesis of cerebral cortex in healthy aging and multiple sclerosis: potential marker of early white matter injury.

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## Introduction

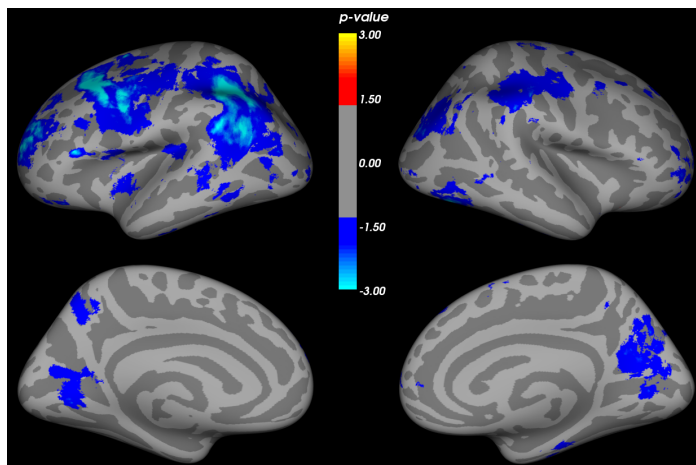
According to the tension-based theory [1], the gyrogenesis of human brain is driven by inter- and intra-gyral axonal connectivity. Consequently, processes such as Wallerian degeneration or axonal injury could affect patterns of cortical folding. In order to assess alterations of the shape and prominence of cortical gyri and sulci, several metrics reflecting area ratio and aggregation of curvature have been proposed. Interpretation of the available curvature based measures may be less intuitive and ambiguous in the presence of cortical atrophy. Therefore, in the present study we explored the local gyrification index (LGI) [2], calculated as a ratio of the cortical surface area and the envelope surface area warped around the exterior of the brain. We hypothesized that LGI may be associated with early white matter (WM) injury in multiple sclerosis (MS) patients.

## Methods

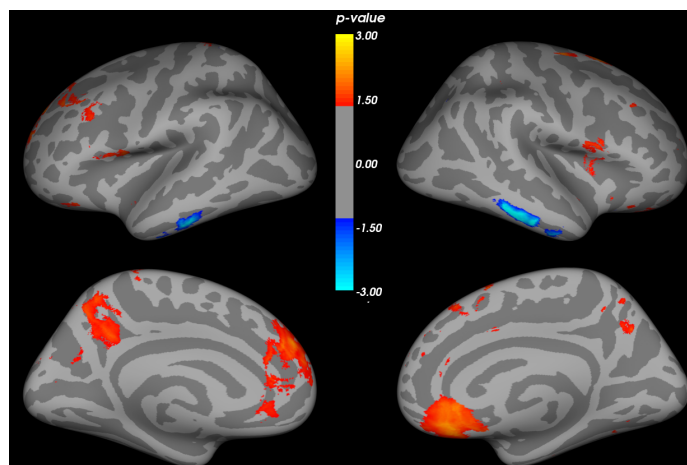
Thirty-six relapsing-remitting MS patients (38±10 years) under ongoing treatment, with disease duration of 5±4 years were scanned on a 3T Philips Achieva using 8-channel head coil. Each MS subject underwent thorough neurological examination and brain MRI including sagittal 3D-MPRAGE sequence (TR/TE/TI = 9.7/4.6/1000 ms,  $\alpha = 8^\circ$ , voxel size 0.8 x 0.8 x 1 mm). Thirty-two right-handed age- and sex-matched healthy controls with mini-mental state examination score 30/30 were selected from the OASIS brains study [3]. These control subjects were scanned on a 1.5T Siemens Vision using sagittal 3D MPRAGE sequence (TR/TE/TI/TD = 9.7/4.0/20/200 ms,  $\alpha = 10^\circ$ , voxel size 1.0 x 1.0 x 1.25 mm, 4 averages). Surface-based cortical reconstruction was performed with FreeSurfer [4] and cortical thickness and LGI were statistically compared between the groups of MS and control subjects, respectively by means of multivariate general linear model. Additionally, correlation between LGI and the expanded disability status scale (EDSS) score was assessed in the MS subjects as well.

## Results

Median EDSS score in the group of MS subjects was 2.5 (0-6.5). Significant ( $p < 0.05$ ) cortical thinning associated with normal aging of the control subjects as well as focal atrophies in MS patients were in accordance with published literature [5, 6]. In the control subjects, LGI had significant ( $p < 0.05$ ) negative age correlation in the large cortical areas of the left frontal and parietal lobes and in a smaller extent in the same areas of the right hemisphere (Fig. 1). Taking age into account, we observed in the MS patients significant ( $p < 0.05$ ) negative LGI correlation with EDSS in inferior temporal cortex bilaterally (Fig. 2). Surprisingly however, the LGI had positive correlation with EDSS in left superior frontal and parietal, anterior rostral cingulate, right orbitofrontal, and focally in the precentral cortices bilaterally, respectively (Fig. 2).



**Figure 1.** Correlation between cortical LGI and age in the healthy control subjects.



**Figure 2.** Correlation between cortical LGI and EDSS (accounting for age) in MS patients.

## Discussion

Thinning of cerebral cortex is well-known phenomenon associated with healthy aging [5]. On top of this, we have observed in the control subjects reduction of LGI with age, which was much more prominent in the left than in the right hemisphere. In the MS subjects on the other hand, we found only focal correlation between reduced LGI and increased disability score, involving inferior temporal cortex bilaterally. Contrary, much larger cortical areas expressed positive correlation with disability. In the light of our hypothesis and the results from control subjects, this observation comes as a surprise. Yet from fMRI experiments, these areas are well known to be associated with functions often affected in MS patients.

## Conclusion

The present data suggest that along the healthy aging, large areas of associative cortices may lose shape and compactness. These changes take place predominantly in the left hemisphere, which is in accordance with idea of lateralization of human brain. In the MS subjects on the other hand, the LGI increased with disability in a several areas of associative cortices. These areas were larger and distinct from those suffering from MS related cortical atrophy [6]. Therefore, LGI may possibly probe for processes of an early irreversible axonal damage, and thus bring more insight into pathology of MS. However, to our knowledge, LGI has not been studied in MS before, and thus the disease mechanisms affecting it must be further explored.

## References

[1] Van Essen D., *Nature* 1997, 385:313; [2] Schaer M. et al.; *IEEE TMI* 2008, 27(2):161; [3] Marcus, DS. et al. *J Cogn Neurosci* 2007, 19:1498; [4] <http://surfer.nmr.mgh.harvard.edu>; [5] Salat, DH. et al. *Cereb Cortex* 2004, 14:721; [6] Sailer, M. et al. *Brain* 2003, 126(9):1734