

Reduced Callosal Thickness and Volume Due to Myelin Deficit in RLS: Thickness Measurement and Volumetric Study

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INTRODUCTION: Restless legs syndrome (RLS) is a sensorimotor disorder characterized by motor restlessness in the presence of uncomfortable sensation of the leg¹. Previous in vivo MR studies have suggested that iron deficiency in the sensory-motor pathway is strongly related to the pathology underlying RLS². Furthermore, autopsy analysis revealed that the levels of myelin-specific proteins were significantly decreased in RLS brain tissues compared to normal control brains, providing evidence of myelin deficit (hypomyelination)³. Since iron plays a crucial role in myelination in the axonal fibers in white matter, we hypothesized that myelin deficit in RLS due to insufficient cerebral iron could cause failure to proper management of sensory-motor function; in particular, corpus callosum (CC) has become an important focus of investigation due to its structure consisting of highly myelinated fibers for fast conduction of sensory-motor information. To test our hypothesis, we developed an image analysis tool that allows for the thickness measurement of CC. We also applied an optimized voxel-based morphometry (VBM) for the volumetric comparison between the study groups.

METHODS: Twenty-three RLS patients with severe status (55.9 ± 2.7 yrs, severity score⁴ of 24.1) and 23 age- and gender- matched normal control subjects (55.7 ± 2.7 yrs) were studied. Paired t-test was used for the between-group comparison of callosal thickness and brain volume. High resolution T1 images (MPRAGE, TR/TE/TI=9.9/4.6/600ms, matrix size=256x256, slice thickness=1mm) were acquired on 3.0T with a 8-channel head coil.

Image analysis for the callosal thickness mapping includes several procedures: segmentation of the white matter, extraction of the medial corpus callosum, distance mapping, parcellation of CC, generation of medial line and measurement of the thickness. First, T1 images are segmented into white matter (WM) using a prior tissue probability map of WM, followed by extraction of a single middle sagittal image of CC via a manual region-of-interest drawing (Fig.1A). Using Euclidean transform, the extracted CC was splitted into a superior (top) and inferior (bottom) line by the selection of two optimal terminal points (t(g) and t(s), Fig.1B) that allows for minimizing difference of the length of each surface boundary. Subsequently the distances between each of 150 equidistant surface points making up the medial CC line and 150 equidistant surface points making up the callosal surface boundaries (top and bottom) were calculated (Fig. 1D). Finally, a statistical color map showing the between-group differences were generated by applying a paired t-test.

For an optimized VBM analysis for WM volume, customized prior tissue probability maps were generated via a linear affine registration. And then all T1 images were segmented into GM/WM/CSF with the generated probability maps using VBM5 toolbox⁶. The segmented WM probability maps were modulated with the Jacobian matrix for volumetric study and smoothed with an isotropic 8 mm FWHM Gaussian kernel. To avoid the false-positive errors, the WM mask generated by optimized threshold value was applied in the statistical analysis.

RESULTS & DISCUSSION: The mean values of callosal thickness in control subjects are consistent with published data⁷, confirming the reliability of distance mapping algorithm. Compared to the controls, the analysis of distance maps revealed a significantly decrease in callosal thickness in the midbody regions in RLS (Fig. 2) in which the axonal fibers are connecting primary motor or somatosensory areas. In addition, the fiber composition of the midbody of CC tends to have higher proportions of coarse-diameter, highly myelinated fibers than other callosal regions. Hence, the decreased callosal thickness may indicate fewer numbers of fibers or a decrease in the myelination of fibers resulting from iron deficiency. VBM analysis found that the callosal volume in RLS patients was significantly decreased compared to controls (Fig. 3), which is consistent with the reduced callosal thickness. In line with VBM finding, we may speculate that impaired iron management in the RLS brains leads to myelin deficit in the sensorimotor fibers, resulting in reduced callosal thickness and volume in the midbody region of CC. This might affect interhemispheric communication channels by affecting brain functional synchrony impairment, and may contribute to the symptoms of RLS. Therefore, the callosal thickness mapping technique can be useful as an in vivo neuroimaging tool for elucidating the underlying mechanism of RLS and for future diagnosis and monitoring of RLS as well as myelin-related WM diseases.

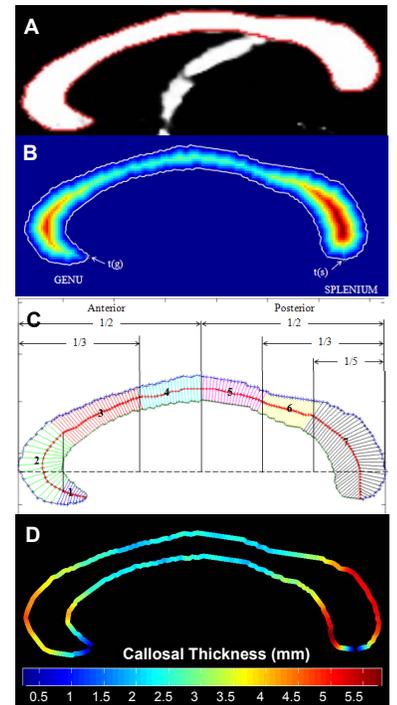


Fig. 1 (A) ROI drawing of a single CC from the segmented WM; (B) Euclidean distance mapping; (C) generation of top/bottom/medial line (red) and parcellation⁵ of CC along equidistant surface points; (D) callosal thickness map from the medial line.

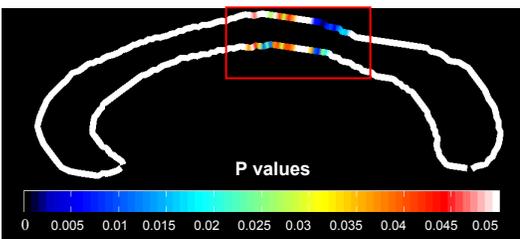


Fig. 2 A color map showing a significant thinner callosal thickness in RLS compared to the controls in the region of mid body regions of CC connecting to primary motor and somatosensory cortex areas (red box, 4-5 in Fig. 1C). A color bar indicates a P value ($P < 0.05$)

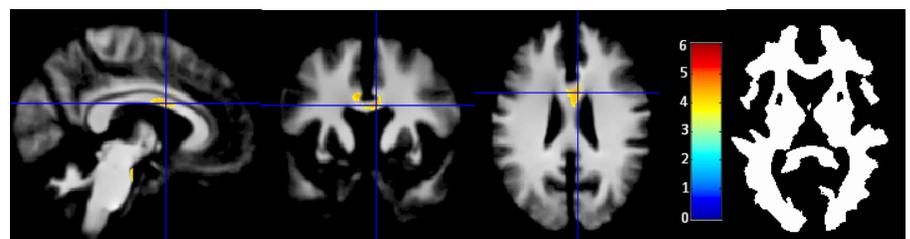


Fig. 3 Optimized VBM analysis for statistical group comparison of the WM brain volume, showing a significant volume reduction in the corpus callosum in RLS patients compared to control group (paired T-test, $P < 0.05$ corrected). Results were displayed by a sagittal, coronal and axial view on the customized white matter template. The WM mask was shown in the last column. A color bar indicates a statistical T-score.

REFERENCES: ¹Ekbom, Neurology 1960; ²Lee et al., ISMRM 2010, 4356; ³Lee et al., ISMRM 2009, 243; ⁴Walter et al., Sleep Med 2004; ⁵Witelson et al., Brain 1989; ⁶VBM5, <http://dbm.neuro.uni-jena.de/vbm/>; ⁷Luders et al., NeuroImage 2007

ACKNOWLEDGEMENT: Supported by grant NIH (1R01AG027771-01A2) and Penn State's Center of Excellence from PA Department of Health (SAP 4100039920)