Alterations of Cerebral Cortical Thickness in the Sensory and Pain Systems in Restless Legs Syndrome

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INTRODUCTION

Restless legs syndrome (RLS) is a neurological disorder characterized by extremely uncomfortable senstations in the limbs prior to uncontrollable urge to move the affected limb [1]. Despite the explicit presence of the sensory and pain symptoms in the patients with RLS, previous neuroimaging studies have not provided supporting evidence to elucidate the mechanism underlying RLS. In this work, we studied whole brain cortical thickness to test the hypothesis that morphological alterations of cortical thickness in the sensory-motor and the central pain system in RLS may be responsible for dysfunction for management of sensory and pain processing. In this study, we applied advanced surface classification methods for accurate measure of cortical thickness, and both a whole brain vertex-wise analysis and a ROI analysis for performing statistical group comparison.

METHODS

A total of 28 RLS patients with severe status (54.8±14.8 yrs, severity score [2] of 25.4±7.2) and 51 age- and gender-matched normal control subjects (60.2±15.3 yrs) were studied. To control pharmacological effects on cerebral morphology, all patients were asked to stop taking medication at least for one week prior to MRI scanning.

MRI data were obtained on a 3.0 T (Philips, Netherlands) with an 8-channel phased array coil. High-resolution T_1-weighted images were acquired using a 3D magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence: TR /TE /TI= 9.87/4.59 /600ms, flip angle= 8°, sense factor= 2, in-plane resolution= 1×1 mm^2, matrix size= 256×256, and FOV= 25×25 cm^2).

Cortical Thickness Analysis:

A. Vertex-wise Analysis: First, the reconstruction of cortical thickness map was done using the Freesurfer software (http://surfer.nmr.mg.harvard.edu/). Briefly, technical procedures includes removal of non-brain tissue, talairach transformation, intensity normalization, tessellation of the gray/white matter boundary, and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders. Once the cortical models are complete, a number of deformable procedures were performed for further data processing and analysis to match cortical geometry across subjects, parcellation of the cerebral cortex into units based on gyral and sulcal structure. Finally, vertex-by-vertex statistical analysis was applied for the group comparison of the whole brain cortical thickness, using SurfStat (http://www.math.mcgill.ca/keith/surfstat/) at the Montreal Neurological Institute (MNI) space. Analysis of covariance (ANCOVA) was performed in order to control the effects of age and gender difference. Multiple comparison correction were taken into account for the vertex data using a false discovery rate (FDR) correction at 0.05 level of significance.

B. ROI-based Analysis: After cortical thickness mapping, all images were aligned to a common surface template and ROI on the template were mapped back to each subject's native image space. Then mean volume and thickness of cortical gray matter in each RIOI were determined and used for statistical analysis. Likewise vertex-wise analysis, ANCOVA was performed for the group comparison to consider differences of age and gender.

RESULTS & DISCUSSION

Compared to controls, both vertex-wise and ROI-based analysis show that the RLS patients exhibit a significantly reduced cortical thickness in the postcentral cortex (somatosensory area, Figs. 1-2) and increased cortical thickness in the cingulate cortex bilaterally (Figs. 1-2) (FDR < 0.05). However, there were no significant differences in gray matter volume of subcortical regions in sensory-motor pathway encompassing basal ganglia except postcentral cortex (data not shown herein). It is of importance to note that the consistent findings from both ROI-based and voxel-wise statistical analysis support compelling evidence of the structural changes in the sensory and pain system, which avoids false positive reports by registration error [3].

Up to date, RLS has been mainly viewed as the sensory-motor disorder, which has been supported by previous neuroimaging studies. For instance, voxel-based volumetric study showed that the cerebral volumes in the mid-sagittal corpus callosum in which fibers connects to sensory-motor regions was significantly decreased in RLS compared to controls [4]. Furthermore, impaired iron management, one of causing factors in RLS, was known to lead to myelin deficit in the sensorimotor fibers[5]. In line with these reports, the involvement of the postcentral gyrus provides another explicit evidence of abnormal processing of sensory information (sensory disturbance), which impedes correct execution of motor program to control a voluntary movement.

In contrast, the increased cortical thickness in the cingulate cortex, a central region of pain system, may reflect the neuroplasticity stimulated by chronic pain sensations in RLS. Therefore, our findings of alteration of cerebral cortical thickness in the sensory and the pain pathway provide new insights for better understanding on the pathophysiology underlying RLS and add a useful surrogate marker for RLS.

REFERENCES: [1] Ekbom, *Neurology* 1960; [2] Walter *et al., Sleep Med* 2004 ; [3] Bookstein Fred., *NeuroImage* 2001; 14: 1454-1462; [4] Lee *et al., Proc. ISMRM* 2009; 19: 243; [5] Connor *et al.*, *Sleep Medicine* 2011; 12: 614-619;

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

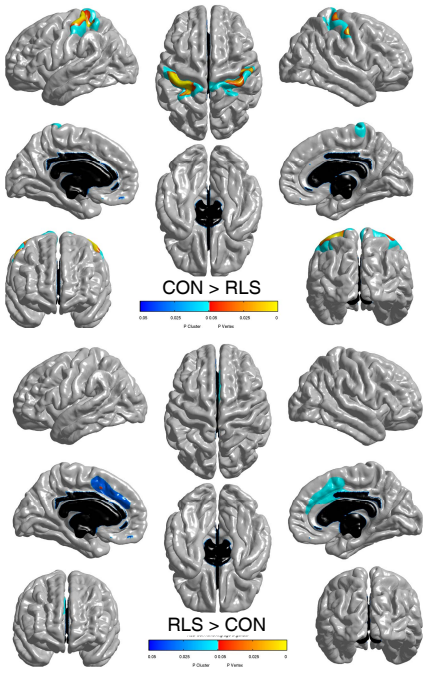
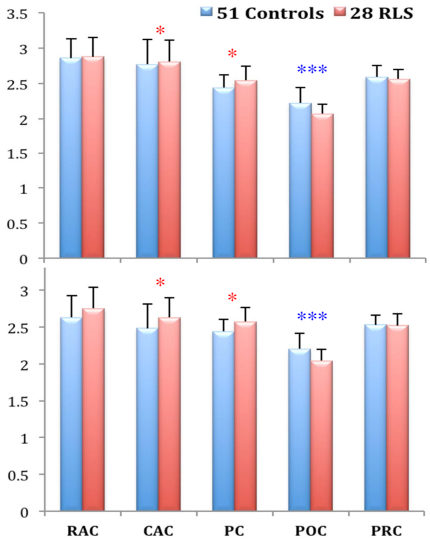


Figure 1. Regional cortical thickness variation showing a cortical thinning in RLS patients (top, CON>RLS) and a cortical thickening (bottom, RLS>CON, corrected *P* value < 0.05). Cooler color represents a cluster level analysis and warmer color represents a vertex level analysis. Left side on the images presents the left hemisphere.



Figures 2. ROI analysis (ANCOVA) for group comparison of cortical thickness (top is for left hemisphere, and bottom is for right hemisphere). Results are means ± SD. * P < 0.05, RLS > CON; *** P < 0.0001, RLS < CON. Abbreviation: RAC, rostral anterior cingulate cortex; CAC, caudal material cingulate cortex; PC, posterior cingulate cortex; POC, postcentral cortex; PRC, precentral cortex.