Multimodality Study for Restless Legs Syndrome: Morphological Changes in White and Gray matter.

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Introduction: Restless leg syndrome (RLS) is a sensory-motor disorder causing chronic sleep disturbances. Currently, neuroradiological investigations such as functional MRI, voxel-based relaxometry (VBR) as well as nuclear medicine have revealed a widespread pattern of pathological changes involving cerebra, cerebella and brain stem [1-3]. Thus, underlying mechanism of RLS is not well-understood. For this reason, the aim of our study was to use multimodality approach to investigate overall morphological changes with voxel-based morphometry (VBM) and white matter changes with diffusion tensor imaging (DTI).

Methods:

Subjects: 27 patients with RLS (54.6±15.3 yrs) and 27 age- and gender-matched controls (54.8±15.0 yrs) were used for VBM study. 7 RLS patients (54.1±19.3 yrs) and age-matched controls (54.4±14.5 yrs) was used for DTI study. The RLS severity (mean 24.4±6.9) was evaluated by using IRLSSG [4]. To minimize drug effects on structural changes, all patients discontinued RLS medication for at least one week prior to MR scanning.

MRI acquisition: High resolution T1-weighted images (MP-RAGE, TR/TE/TI=9.9/4.6/600ms, matrix size=256×256, slice thickness=1mm) were acquired on a 3.0 T system (Philips Medical). The DTI images were acquired with single-shot spin-echo EPI, SENSE factor 2.5 and 32 diffusion gradient directions with b value=1000s/mm^2. Fractional anisotropy (FA) maps were calculated from DTI data set after eddy current correction using FSL [4].

Data processing & Statistics: For VBM analysis, all images were segmented into GM, WM, and cerebrospinal fluid (CSF) with tissue probability maps using VBM5 toolbox [5]. After segmentation, the final tissue maps of GM, WM and CSF were modulated with the Jacobian determinants deformation parameters in order to analyze volume differences between study populations. Finally, the modulated tissue maps were smoothed with a 9 mm WHM Gaussian kernel and entered statistical analysis. Paired-t test was used for the mean comparison of the two groups. A significance level was set at corrected $p < 0.05$ (cluster level) or uncorrected $p < 0.001$ (voxel level).

Results: VBM results demonstrated a significant decrease in the motor areas of both gray and white matter (somatosensory and primary motor cortex) in the Figs. 1-2. DTI results showed that decreased FA was found in the white matter regions of RLS patients that are close to motor cortex (precentral, superior, and middle frontal gyrus, Fig. 3).

Discussion & Conclusion: In this study, much care was taken to avoid any possible confounding factors such as age and gender in order to explore the subtle pathological changes of RLS. Using paired t-test with close age-matched controls, we revealed a decrease in volume in motor regions and FA reduction in cortical-spinal tracts in RLS. The observation of morphological changes in gray matter and FA changes white matter involving motor functions suggest a more profound pathology in RLS. Considering our previous studies showing iron deficiency from the same study cohort [3], it is likely that the FA reduction may indicate a hypomyelination since iron is known to involve in myelination process. This will, in turn, leads to atrophic changes in the associated brain regions. Our data provide an important link for understanding the pathogenesis of RLS. The fusion of the two image modalities from the same study cohort is effective and efficient in acquiring data for elucidating the underlying mechanism of RLS and for future diagnosis and monitoring of the disease.

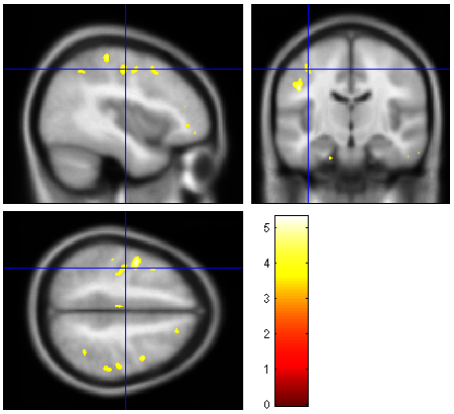

Fig. 1 Volumetric decreases in gray matter regions in RLS mainly including primary motor areas displayed at $p < 0.001$, uncorrected.

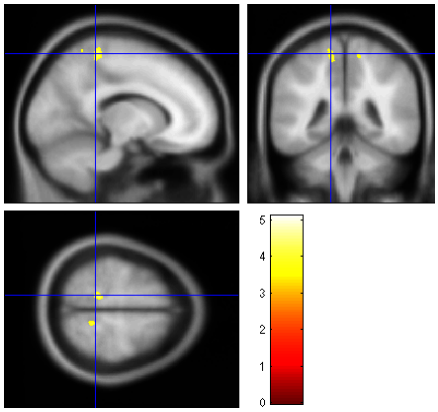

Fig. 2 Volumetric decreases in white matter regions in RLS close to motor areas at $p < 0.001$, uncorrected.

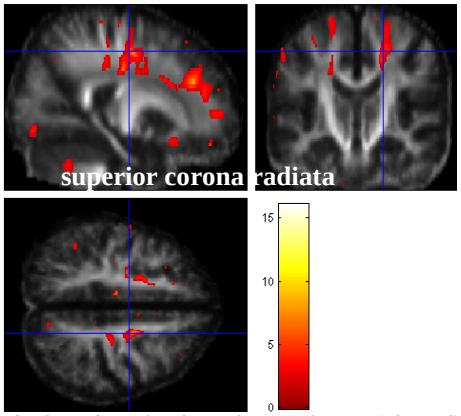

Fig. 3 Regions showing a decreased DTI FA in RLS overlaid on the averaged FA maps of all subjects in different views. A color bar represents a T score

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