QUANTITATIVE SUSCEPTIBILITY MAPPING (QSM) INDICATES POSSIBLE IRON DEFICIENCY IN THE THALAMUS AND DENTATE NUCLEUS IN RESTLESS LEGS SYNDROME (RLS)

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PURPOSE: Restless legs syndrome (RLS) is a common neurological disorder of major clinical and public health significance in the western world. It is characterized by unpleasant sensations mainly in the legs and an urge to move during sitting or resting in the late part of the day[1]. Previous studies have associated RLS to the abnormal dopaminergic function in the central nervous system (CNS) and dysfunction in iron metabolism[2-5]. Non-invasive accurate assessment of regional brain iron status is therefore believed to give important implication on the pathophysiology of the disease and for assessing potential iron therapies. Recent developments in high resolution MRI[6] and quantitative susceptibility mapping (QSM)[7-15] have made it possible to obtain ultra-high resolution maps of tissue magnetic susceptibility which, as shown in previous postmortem and *in vivo* human studies[14,15], correlates well with tissue iron concentrations in brain gray matter. Therefore in this study we investigated selected deep brain structures that are potentially affected by iron deficiency in RLS using QSM.

METHODS: 56 subjects (26 controls and 30 RLS patients) were scanned at 7T (Philips Healthcare) using a 32-channel Nova medical receiver head coil. Two subjects were scanned with a 3D multi-echo GRE sequence with 1mm isotropic resolution, TR/TE1/ΔTE=45/2/2 ms, 9 echoes, flip angle of 9°, bandwidth 1530 Hz/px. The other 54 subjects were scanned with a 3D single-echo GRE sequence with 0.8 mm isotropic resolution, TR/TE= 20/12 ms, flip angle 10°, bandwidth 169 Hz/px. For all the scans, MR phase data at TE=12 ms were used to generate quantitative susceptibility maps. Phase data was first unwrapped with a Laplacian-based phase unwrapping method[12]. The background gradient was then removed using the SHARP method with kernel size of 4 mm and with tsvd threshold set to 0.05[11]. QSM images were then generated using the LSQR method[12]. The QSM image of each subject was coregistered to the QSM image in the 'Eve' atlas created in the Johns Hopkins University using linear and non-linear transformations[14]. After that, the brain parcellation map was transformed to the subject space and adjusted if necessary by a radiologist (HL). The QSM image was referenced with respect to the CSF in the lateral ventricle. Regions of interest (ROI) including substantia nigra (SN), red nucleus (RN), dentate nucleus (DN), caudate nucleus (CN), putamen (PUT), globus pallidus (GP), thalamus (Thal) and pulvinar (Pul) were then selected for quantitative comparison between the normal control and RLS patient groups. A one-tailed two-sample t-test was used to test the directional hypothesis that RLS patients have less iron than normal control groups in the selected ROIs. In order to identify potential substructures in the selected ROIs that are affected by iron deficiency, all the QSM images were also normalized to the Eve atlas space for a voxel-based statistical analysis. Two-sample t-test with a significance p-value of 0.05 was used for the voxel-based analysis.

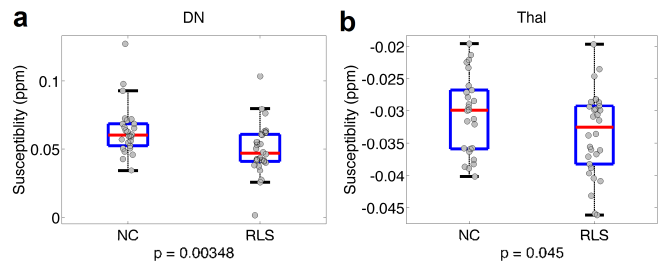

Fig. 1. Box plot showing significant decreased susceptibility in RLS group as compared to normal control (NC) group in (a) the dentate nucleus (DN) and (b) Thalamus (Thal).

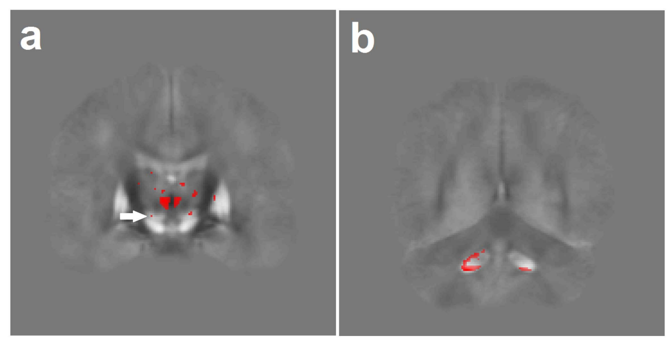

Fig. 2. Deep gray matter regions with significantly decreased susceptibility (red indicates p-value thresholded t-statistics) overlaid on the mean quantitative susceptibility maps of the normal control group normalized to Eve atlas space. A) White arrow points to the right sub-thalamic nuclei (STN). B) dentate nucleus effects. Gray scale of the images is -0.15 to 0.15

RESULTS: The two groups studied were well matched for age with RLS patients of 58.9±10.1 y/o and normal controls of 58.1±8.5 y/o. The comparison of the magnetic susceptibility values between the two groups in selected gray matter ROIs showed significant differences in the DN ($p<0.01$) and in the thalamus ($p<0.05$) (Fig. 1). No significant differences between control and RLS patient groups was found in other selected ROIs. Such regional differences were also visible in the voxel-based analysis (Fig. 2) with most highlighted regions in the DN and Thalamus. Susceptibility differences in certain substructures such as the sub-thalamic nuclei (STN) (white arrow in Fig. 2) were also visible.

DISCUSSION: Previous RLS studies have indicated that SN is the main region affected by iron deficiency in RLS[4], yet such difference was not found between the RLS and control group in this QSM study. The observed significant difference in DN partly agrees with a previously fMRI study suggesting the cerebellum involvement during RLS sensory symptoms[16]. In addition, the voxel-based analysis done in this study suggests further parcellation of the thalamus may be needed to further confirm the local regions affected by possible iron deficiency in RLS.

CONCLUSION: This QSM study shows that dentate nuclei and thalamus may be affected by iron deficiency in RLS.

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