ASSESSMENT OF BRAIN IRON DEFICIENCY IN RESTLESS LEGS SYNDROME (RLS) USING QUANTITATIVE SUSCEPTIBILITY MAPPING AT 7T

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TARGET AUDIENCE: Researchers and clinicians interested in restless legs syndrome and quantitative susceptibility mapping.

PURPOSE: Restless legs syndrome (RLS) is a neurological disorder that is characterized by an urge to move the legs, which is usually accompanied or caused by unpleasant sensations in the legs[1]. Previous studies on cerebrospinal fluid (CSF)[2] and brain MRI[3-5] have suggested that iron insufficiency in the central nervous system (CNS) may play an important role in the pathology of RLS through the dopaminergic system. Thus mapping the brain tissue iron concentration could give important clues in understanding the pathophysiology of RLS. Previous MRI studies on RLS mainly used R2* or R2'[3-4] and very recently MR phase[5] as tissue iron index. High-pass filtered MR phase data commonly used in susceptibility weighted imaging (SWI) can reveal important information on tissue iron concentrations, however the phase quantities processed in conventional SWI depend strongly on the high-pass filter setup[7] and the contribution of background field gradients and therefore are not very quantitative measure of tissue magnetic susceptibility, the fundamental physical property of tissue that phase contrast is based on[6]. On the other hand, recent developments in quantitative susceptibility mapping (QSM)[7-15] have made it possible to obtain ultra-high resolution maps of tissue magnetic susceptibility. Several studies have shown that paramagnetic tissue iron is the predominant source of the susceptibility measures in gray matter[6] and that its concentration correlates very well with magnetic susceptibility values measured in postmortem and *in vivo* human brain tissues[14, 15]. Therefore in this study we are testing the hypothesis of brain iron deficiency in RLS patient using QSM.

METHODS: 19 subjects (5 controls and 14 RLS patients) were scanned at 7T (Philips Healthcare) using a 32-channel Novamedical receiver head coil as part of an ongoing RLS study. Two subjects were scanned with a 3D multi-echo GRE sequence with 1mm isotropic resolution, 220x220x110 mm^3 field of view (FOV) with axial slab orientation, TR/TE1/ΔTE=45/2/2 ms, 9 echoes, SENSE factor of 2.5x1x2, flip angle of 9°, bandwidth 1530 Hz/px, scan time 5:15 min. The other 17 subjects were scanned with a 3D single-echo GRE sequence with 0.8 mm isotropic resolution, 220X220X140 mm^3 field of view (FOV), TR/TE= 20/12 ms, SENSE factor of 2.5x1x2, flip angle 10°, bandwidth 169 Hz/px, scan time 4:38 min. 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 LDDMM transformation[14]. After that, the brain parcellation map containing 163 segmented brain structures defined in the Eve-atlas 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. We also investigated the susceptibility values in two major white matter (WM) fibers, i.e. corpus callosum (CC) and corona radiata (CR). A one-tailed t-test was used to test the directional hypothesis that RLS patients have less iron than normal control groups in the selected ROIs.

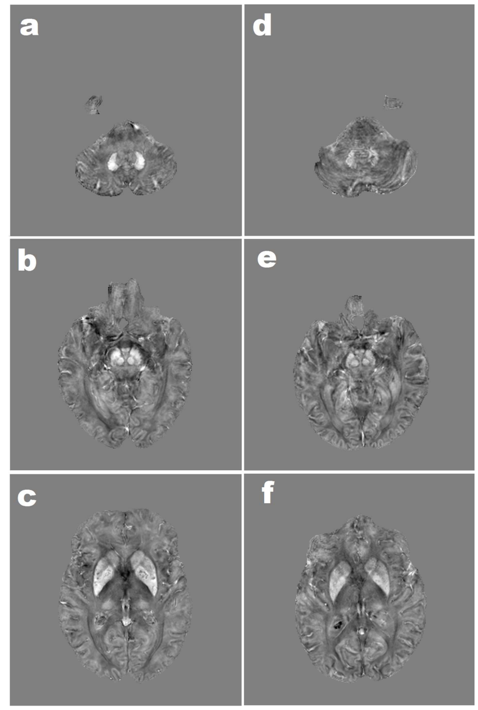

Fig. 1 Quantitative susceptibility maps of a 69-year-old normal control (a-c) and a 69-year-old RLS patient (d-f) showing brain areas of interest, e.g. dentate nucleus (a, d), substantia nigra and red nucleus (b, e), caudate nucleus, putamen, globus pallidus and thalamus (c, f). The gray scale in all the images ranges from -0.15 (black) to 0.15 ppm (white).

RESULTS: The two groups studied were well matched for age with RLS patients of 56.9±11.3 y/o and normal controls of 58.6±8.4 y/o. Figure 1 shows some example QSM images of a 69 y/o normal control (a-c) and a 69 y/o RLS patient (d-f) with 0.8 mm isotropic resolution. As shown in Fig. 1, QSM images give very good tissue contrast of the iron-rich deep nuclei, e.g. DN, SN, RN, CN, GP, PUT and the pulvinar nucleus in the thalamus, which are areas of interest for RLS. The comparison of the magnetic susceptibility values between the two groups in selected gray matter ROIs is shown in Fig. 2. Overall, a decreased magnetic susceptibility is observed in RLS group as compared to the control group in SN, RN, DN, GP and pulvinar. Among them the difference is significant in the DN within the tested group ($p<0.05$), while the difference in SN showed a trend ($p<0.12$). No significant difference between control and RLS patient groups was found in selected WM regions.

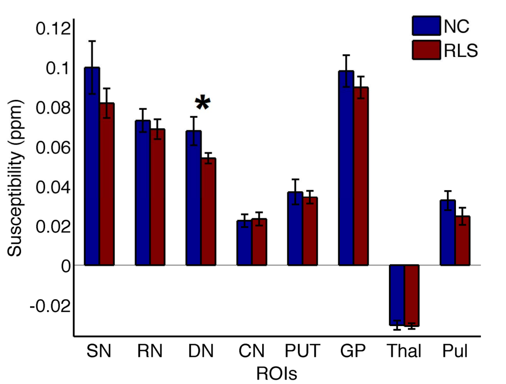

Fig. 2 Comparison of susceptibility values in selected ROIs in the normal control (n=5) and RLS (n=14) groups. Error bar indicates inter-subject standard error. *: $p < 0.05$.

DISCUSSION: In order to answer more specific questions related to the pathology of RLS with more statistical power, MR measurements on more subjects, especially normal controls, will need to be added to the study. In addition, the measured tissue susceptibility values need to be analyzed together with other clinical measures, e.g. disease onset and RLS severity scores, which is ongoing.

CONCLUSION: Magnetic susceptibility measured using QSM has potential in the assessment of brain iron deficiency.

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