

Reduction of $R2^*$ in the Basal Ganglia of Restless Legs Syndrome: a Biomarker for Iron Deficiency

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Introduction:

Restless legs syndrome (RLS) is a neurological disorder with a prevalence of about 5-10% of the general population. Its clinical symptom is characterized by uncontrollable, unbearable urges to move the legs, causing chronic sleep deprivation. The iron deficiency has been considered an important contributing factor for RLS [1]. *In vivo* iron evaluation for RLS has largely utilized T2 ($=1/R2^*$). However, other confounding factors such as water contents and diffusion may result in changes in tissue T2. Tissue iron content is known to be more specifically associated with tissue $R2^*$ ($=1/T2^*$). The purpose of this study is two-fold: 1) to determine the sensitivity of $R2^*$ mapping method for the detection of the iron deficiency in RLS, and 2) to determine abnormal $R2^*$ distribution in the nigro-striatal dopaminergic pathway.

Methods:

Subjects: 24 RLS (8 male 16 female, mean age 52.4 ± 14.3 yrs) and closely age- and gender-matched normal subjects (8 male 16 female, mean age 52.9 ± 15 yrs) were studied. RLS was assessed clinically using the international restless legs syndrome study group (IRLSSG) rating scale [2] with mean score = 23.7 ± 7.0 . To eliminate drug effects, all of RLS patients stopped taking the medication at least for one week prior to MR scanning.

MRI: $R2^*$ mapping was performed on a 3.0 T scanner (Philips Medical) with 14 gradient echo images with TE = 3.7 ms, inter echo delay = 3.3 ms, TR = 311 ms, matrix size = 256×256 , slice thickness/number = 1mm/ 40, and FOV = $23 \times 23 \text{cm}^2$ in 6 min 40s.

Data processing & Statistics: For voxel-based statistical analysis, statistical parametric method (SPM5) [3] was used. First, $R2^*$ maps generated by home-developed software were spatially normalized and co-registered into the Montreal Neurological Institute space using a template created by averaging $R2^*$ maps of the study cohort. Subsequently, co-registered $R2^*$ maps were re-sampled by tri-linear interpolation to a final voxel size of $0.9 \times 0.9 \times 2 \text{mm}^3$. The spatially normalized images were smoothed with a Gaussian kernel of $4.5 \times 4.5 \times 4 \text{mm}$ FWHM. To minimize of $R2^*$ dependence on age [4], paired-t test was applied for group mean comparison between the two groups. $P < 0.05$ will be considered as a statistical significance.

Results:

Fig. 1 shows a comparison of $R2^*$ map of a typical RLS to an age-matched control, demonstrating a prominent $R2^*$ reduction in basal ganglia. Brain tissue iron is known to increase with age [5]. As demonstrated in Fig. 2, $R2^*$ increases with age in the basal ganglia within control subjects (linear regression, $p < 0.05$). Fig. 3 revealed a significant $R2^*$ decrease in basal ganglia of RLS patients, indicating reduced iron content compared to normal control group (paired *t*-test, $p < 0.05$).

Discussion & Conclusion:

Our voxel-based comparison of $R2^*$ was capable of detecting brain tissue iron changes in the BG in normal and disease conditions. Iron plays an important role in dopaminergic function. Thus, the iron deficiency of BG in RLS observed in this study is likely, in part, related to the decreased dopamine synthesis in RLS [6]. These finding support the hypothesis that insufficient iron level in the subcortical structures (BG, RN) of RLS patient leads to the dysfunction in the sensory-motor pathway that is responsible for body movement. Our data show that voxel-based $R2^*$ map is sensitive for detection and evaluation of local change of brain iron level and, therefore, valuable clinically for diagnosis and monitoring RLS and scientifically for elucidating the underlying mechanism of the disease.

References:

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Acknowledgement:

Grants support: Penn State's Center of Excellence from PA Department of Health (SAP 4100039920), NIH (1R01AG027771-01A2)

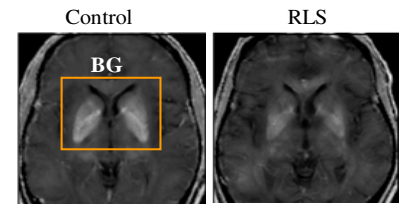


Figure 1 $R2^*$ maps showing the hypointensity in the basal ganglia (BG) of a young patient with RLS compared to an age-matched control subject

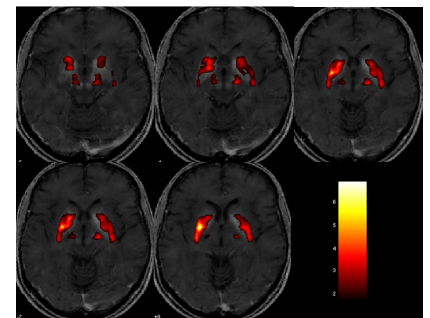


Figure 2 Increase in $R2^*$ with age in the basal ganglia and substantia nigra within a control group (linear regression, $p < 0.05$)

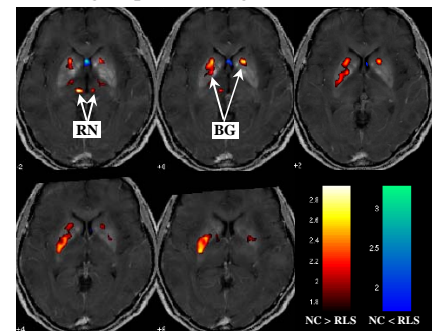


Figure 3 A significant $R2^*$ decrease in RLS (control $>$ RLS, warm color bar (left) at $p < 0.05$). T values of voxels within significant clusters were overlaid of $R2^*$ image of a control subject.