

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

B-Y. Lee¹, E. Farace², X. Sun³, J. R. Connor², and Q. X. Yang^{1,3}

¹Bioengineering, The Penn State University, Hershey, PA, United States, ²Neurosurgery, The Penn State University, Hershey, PA, United States, ³Radiology, The Penn State University, Hershey, PA, United States

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 = 23×23cm² 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 0.9×0.9×2mm³. The spatially normalized images were smoothed with a Gaussian kernel of 4.5×4.5×4mm 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:

- [1]. Ekbom KA, 1960, *Neurology* 10, p 868-873
- [2]. Water TC *et al.*, 2003. *Sleep Med.* 4, p 121-132
- [3]. Ashburner J *et al.*, 2000, *Neuroimage* 11, p 805-821
- [4]. Vymazal J *et al.*, 1996, *Magn Reson Med* 35, p 56-61
- [5]. Hallgren B *et al.*, 1958, *J. Neurochem* 3, p 41-51
- [6]. Ward RJ *et al.*, 1995, *Biochem Pharmacol* 49, p 1821-1826

Acknowledgement:

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

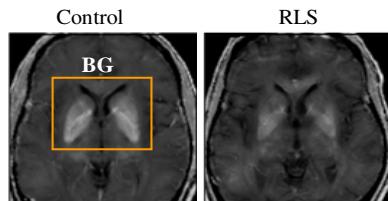


Figure 1 R2* maps showing the hypointensity in the basal ganglia (BG) of a young patient with RLS compared to an age-matched control subject

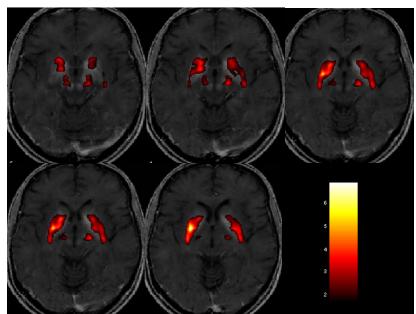


Figure 2 Increase in R2* with age in the basal ganglia and substantia nigra within a control group (linear regression, $p < 0.05$)

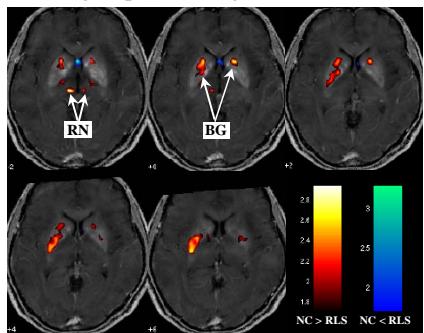


Figure 3 A significant R2* decrease in RLS (control > RLS, warm color bar (left) at $p < 0.05$. T values of voxels within significant clusters were overlaid of R2* image of a control subject.