In vivo Measurement of Iron Deficiency in Restless Legs Syndrome (RLS) with Voxel-Based R2 Relaxometry

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Introduction

Restless leg 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, resulting in nocturnal insomnia and chronic sleep deprivation. The iron deficiency has been considered an important contributing factor to cause RLS [1]. However, abnormality in brain iron distribution in RLS has not been characterized. 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 RLS brain.

Methods

Subjects: Sixteen RLS subjects (55.3 ± 12.0 yrs) and sixteen age-matched normal volunteers (49.6 ± 13.3 yrs) were recruited into this study. RLS severity scores were assessed by the International Restless Legs Syndrome Study Group (IRLSSG) rating scale after discontinuation of RLS medication for at least one week.

MRI: A fourteen echo multi spin-echo sequence was used on a 3 T scanner (Integra, Philips) with TE and inter echo delay = 8 ms, TR = 3792 ms, matrix = 256×256, 30 axial slices, slice thickness = 4 mm, FOV = 23 × 23 cm^2 (0.9 × 0.9 mm^2 voxel).

Data processing: R2 maps were generated by home-developed software using a linear regression method. Spatial normalization was achieved by co-registration of each R2 map into the Montreal Neurological Institute space [2] using a R2 template created by averaging the R2 maps of the study cohort. Subsequently, co-registered images were re-sampled by tri-linear interpolation to a final voxel size of 0.9 × 0.9 × 2 mm^3. The spatially normalized images were smoothed with a Gaussian kernel of 2.5 × 2.5 × 5 mm^3 FWHM.

Statistics: Comparison between two study groups, and correlation between R2 and RLS clinical severity were conducted using a two-sample t-test and a simple linear regression respectively in SPM2 [3].

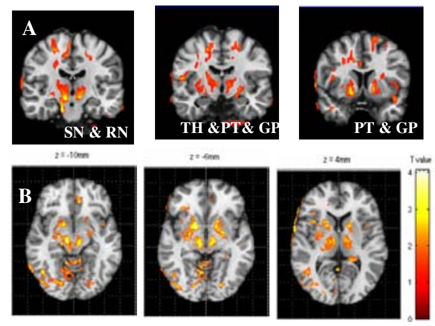

Figure 1. The statistical map of R2 reduction in RLS brain compared to normal age-matched controls ($p < 0.05$) in coronal view (A) and axial view (B).

Results

Voxel based relaxometry (VBR): The statistical map in Fig.1 shows a significant R2 decrease in RLS in the basal ganglia and thalamus which are known to have high iron concentration. The regions with significant R_2 reduction in RLS were found in the bilateral globus pallidus (GP), substantia nigra (SN), red nucleus (RN), putamen (PU) and thalamus (TH) (two-sample t-test, cluster level $p < 0.05$). No brain areas were found to have higher R2 in the RLS group than in controls, indicating a consistent trend of reduced R2 in the RLS brain. The R2 reduction in the structures identified by the VBR analysis is further evaluated quantitatively with a region of interest (ROI) study (Table 1).

Correlation between R2 and RLS Symptomatology: As shown in Fig. 2, a significant negative correlation was found between the IRLSSG score and R2 in the substantia nigra (Left: R^2 = 0.4145, p = 0.037; Right: R^2 = 0.3164, p = 0.02). Similar correlation was also found in the right putamen (R^2 = 0.3699, p = 0.001).

TABLE 1. ROI results

Region	Side	RLS Subjects R2 (s^{-1})	RLS Subjects No. voxels	Normal Controls R2 (s^{-1})	Normal Controls No. voxels	P value
RN	L	13.88 ± 0.74	108	14.67 ± 1.00	100	0.017
	R	14.11 ± 0.63	97	14.88 ± 1.08	92	0.017
SN	L	15.07 ± 0.59	112	15.84 ± 0.78	108	0.009
	R	15.44 ± 0.44	80	15.92 ± 0.69	99	0.025
TH	L	13.01 ± 0.43	1776	13.45 ± 0.64	1621	0.024
	R	13.01 ± 0.44	1748	13.45 ± 0.67	1717	0.028
GP	L	16.35 ± 0.77	734	17.41 ± 0.92	609	0.002
	R	16.50 ± 0.66	686	17.17 ± 0.81	678	0.015
PU	L	14.35 ± 0.69	1205	14.83 ± 0.67	1314	0.044
	R	14.38 ± 0.78	1580	14.65 ± 0.68	1369	0.120
CN	L	12.74 ± 0.46	396	13.03 ± 0.51	381	0.069
	R	12.81 ± 0.53	363	13.04 ± 0.41	434	0.128

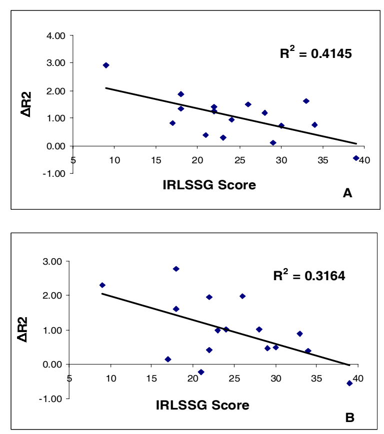

Figure 2. Linear correlation of RLS severity with R2 reduction in the left (A) and right (B) substantia nigra.

Discussion

In this study, we demonstrated that VBR is a sensitive method to quantify the iron changes in the brain associated with RLS. Our data demonstrated a more widespread iron deficiency of RLS subjects in the dopaminenergic neuronal pathway than previous results [4]. The significant negative correlation of iron content decrease in the substantia nigra and putamen with the subjects' clinical severity, suggesting that R2 mapping may be potentially used as a biomarker for the evaluation of this disease.

References

1. Ekbom KA, 1960, Neurology 10, 868-873
2. Collins DL et al., 1998, IEEE Trans Med Imaging 19, 463-468
3. Friston KJ et al., 1994, Human Brain Map 1, 153-171
4. Allen RP et al., 2001, Neurology 56, 263–265