Voxel-based Morphometry Study in Restless Legs Syndrome (RLS): Volumetric Increase in Multiple Brain Regions

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INTRODUCTION:

Restless leg syndrome (RLS) is a sensory-motor disorder characterized by uncontrollable, unbearable urges to move the legs. A body of data has reported iron deficiency in patient with RLS [1-2]. It is well known that gray and white matter volumes in Parkinson's disease (PD) are low compared to normal control due to atrophy which is linked with high iron accumulation in the PD brain. However, it is not known whether or not RLS brain volume is different from normal control. A recent report suggests that volume of the thalamus was higher in RLS brains [3]. In addition, our previous iron study with MRI demonstrated the overall iron deficiency in the deep gray and white matter regions in RLS [4]. Thus, these facts led to the hypothesis that insufficient iron concentration in RLS may contribute to the global regional change. To enhance the sensitivity and reliability to identify volumetric difference between RLS and normal control, we conducted a voxel-based morphometry (VBM) study on RLS.

METHODS:

Subjects: 19 patients with RLS (mean age 53.6 ± 13.5yrs) and 21 age- and gender-matched healthy volunteers (mean age 52.5±16.9 yrs) were studied. RLS severity was evaluated using the IRLSSG rating scale after discontinuation of RLS medication for at least one week.

MRI: T_1-weighted images with high resolution (MP-RAGE sequence, TR=9.9ms, TE=4.6ms, matrix size=256×256, TI=600ms, slice thickness=1mm) were acquired on a 3.0 T system (Intera, Philips Medical). The voxel size was 1×1×1 mm.

Data processing & Statistics: Image processing for voxel-based morphometry was done using SPM2 [5]. Modulated images were used for the volumetric measurement between the two study groups using a two-sample t-test. A significance level was $p < 0.05$ (corrected in cluster level).

RESULTS:

The SPM results in table 1 show a significant focal volumetric change in the gray matter regions (two sample t-test, corrected P<0.02) and white matter regions (corrected P<0.03). In the Figs 1-2, bilateral volumetric increase was found in the gray and white matter in the RLS brain. The involvement of increase in white matter in RLS has not been previously reported.

DISCUSSION & CONCLUSION:

The bilateral thalamic gray matter change was consistent with previous reports. Furthermore, our data demonstrated that overall gray and white matter brain regions showed a significant volume increase in RLS brain. It is of importance to note that most RLS patients (13 among 19) have not taken any RLS medication, which allows for minimizing the drug effect on structural changes. Thus, we may speculate that iron deficiency contributes to the increase in volume in RLS patients compared to controls.

Table 1. Results from voxel-based morphometry

area	cluster level		voxel level		coordinates		
	size (k)	P (corrected)	T value	P (uncorrected)	x	y	z
Increased gray matter in RLS							
Inferior frontal gyrus (L)	233	0.004	4.46	0.000	-40	12	26
Inferior frontal gyrus (R)	33	0.004	3.55	0.001	56	25	28
Anterior cingulate gyrus (L)	461	0.003	4.17	0.000	-4	11	29
Thalamus (R)	8	0.005	3.42	0.001	17	-13	17
Thalamus (L)	21	0.020	2.80	0.004	-14	-16	9
Increased white matter in RLS							
Superior occipital lobe (L)	401	0.003	3.69	0.000	-21	-59	34
Inferior temporal lobe (L)	120	0.005	4.06	0.000	-53	-44	-18
Cingulate lobe (L)	1496	0.024	3.24	0.001	-20	1	34

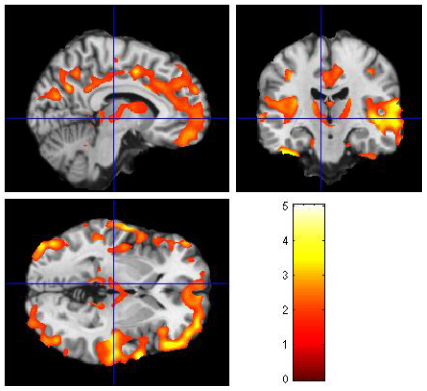

Fig. 1 VBM analysis showing areas that are increased in gray matter bilaterally in RLS at P <0.05:

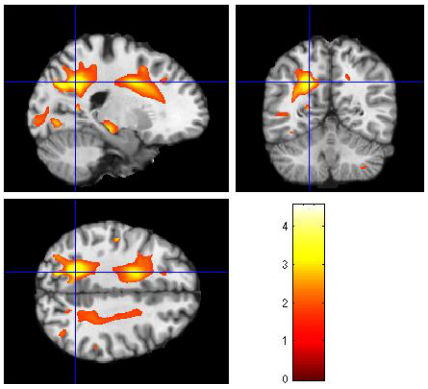

Fig. 2 Areas showing a statistically regional increase in white matter in RLS at P <0.05

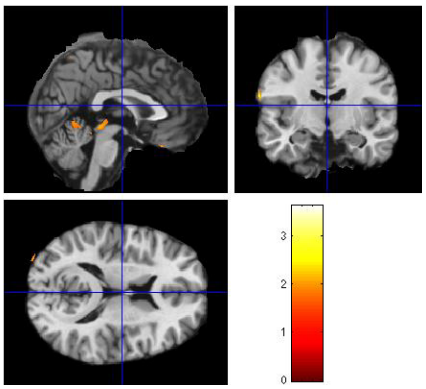

Fig. 3 Inverse contrast showing no areas with a regional increase in controls at P <0.05

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