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Original Article

Mapping intrinsic functional brain changes and repetitive transcranial magnetic stimulation neuromodulation in idiopathic restless legs syndrome: a resting-state functional magnetic resonance imaging study

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ABSTRACT

Objective: The objectives of this study were, first, to explore differences in brain activity between normal people and idiopathic restless legs syndrome (RLS) patients during asymptomatic periods; and, second, to determine whether administering repetitive transcranial magnetic stimulation (rTMS) to specific cortical regions would reverse any observed differences in brain activity and alleviate patient symptoms.
Methods: Fifteen idiopathic RLS patients (nine drug-naive patients) and 14 gender- and age-matched healthy controls were enrolled. Resting-state functional magnetic resonance imaging was used to measure the amplitude of low-frequency fluctuations (ALFF) in spontaneous brain activity during asymptomatic periods. Seven patients received high-frequency (5 Hz) rTMS directed toward the leg area of the primary motor cortex. Scores on the International Restless Legs Syndrome Study Group (IRLSSG) Rating Scale and ALFF values were measured before and after treatment.
Results: Compared with healthy controls, RLS patients showed lower ALFF in the sensorimotor and visual processing regions, and higher ALFF in the insula, parahippocampal and hippocampal gyri, left posterior parietal areas, and brainstem. These results were largely conserved when only drug-naive patients were considered. After rTMS treatment, ALFF in several sensorimotor and visual regions were significantly elevated and IRLSSG Rating Scale scores decreased, indicating improved RLS symptoms.
Conclusions: High-frequency rTMS delivered to the leg area of the primary motor cortex may raise functional activity in the sensorimotor and occipital regions, leading to improve symptoms in RLS patients. These results provide novel insight into RLS pathophysiology and suggest a potential mechanism for rTMS therapy in idiopathic RLS patients.

1. Introduction

Restless legs syndrome (RLS) is a sensorimotor disorder that consists of idiopathic RLS (without known cause) and secondary RLS, which is associated with iron deficiency, uremia, and peripheral neuropathy. Key features include an unpleasant sensation in the lower limbs that appears or worsens during the night and disappears or improves with movement [1]. Although the pathophysiology of idiopathic RLS remains incompletely understood, several studies suggest that it is related to central nervous system abnormalities [2–5]. Three self-evoked, event-related functional magnetic resonance imaging (fMRI) studies reported activation in the cerebellum, thalamus, brainstem, precentral gyrus, and primary somatosensory cortex during symptomatic periods [3–5]. The question arises as to whether or not patterns of functional activity change during asymptomatic periods. Resting-state fMRI, a promising neuroimaging technique that noninvasively measures spontaneous/intrinsic brain

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activity [6], has been widely used to study healthy and diseased brain function. Zang et al. [7] proposed using the amplitude of low-frequency fluctuations (ALFF; calculated as the square root of the power spectrum in a frequency range, usually 0.01–0.08 Hz) to assess the amplitude of resting-state spontaneous brain activity. By measuring the ALFF, researchers have found altered baseline brain activity in patients with attention-deficit/hyperactivity disorder [7] and post-traumatic stress disorder [8]. These recent studies indicate that the ALFF is physiologically meaningful and reflects intrinsic or spontaneous neuronal activity in the brain. Thus, measuring the ALFF during asymptomatic periods and comparing it to that of control subjects might reveal regions of altered functional activity in RLS that may be the basis for the development of symptoms.

Due to the augmentation of RLS symptoms during long-term treatment with dopaminergic medications, we urgently need new therapeutic methods. Repetitive transcranial magnetic stimulation (rTMS) is a newly developed noninvasive technique that can modulate brain function by improving cortical plasticity and can be used to treat some neurological disorders [9–11]. Currently, the consensus is that high-frequency rTMS is excitatory, whereas low-frequency rTMS is inhibitory [12]. Here, we investigated whether or not excitatory rTMS could be used to therapeutically alter brain function in RLS patients. First, we used resting-state fMRI to search for brain regions for which the ALFF values differed between RLS patients and normal controls. Then we used rTMS to modulate one of the cortical regions with altered ALFF values, and we assessed the effect on RLS symptoms.

2. Methods

2.1. Subjects

Fifteen right-handed idiopathic RLS patients (12 females and three males; age range: 35–72 years; mean age: 56.53 ± 9.75 years; nine drug-naive patients) (Table 1) participated in the study. RLS was diagnosed through clinical interview by a neurologist with sleep medicine expertise (Y.H.) and according to the International Restless Legs Syndrome Study Group (IRLSSG) criteria [1]. Severity was scored on the IRLSSG Rating Scale and the Johns Hopkins Restless Legs Severity Scale. We also used the Pittsburgh Sleep Quality Index (PSQI) to assess sleep quality. We scored patients on the Hamilton Anxiety Rating Scale (HAM-A) and Hamilton Depression Rating Scale (HAM-D, respectively) to exclude patients with serious anxiety (score > 21) or depression (score > 20). In addition, we excluded patients with a history of alcohol or drug abuse, anemia, renal disease, spinal cord or nerve root injury, or other neuropathies or sleep disorders. All patients had normal results on general medical and neurological examinations. Routine laboratory test results (including serum levels of hemoglobin, iron/ferritin, urea, creatinine, vitamin

Table 1
Demographic and clinical data in idiopathic RLS patients and healthy controls.

Group	Sex	Age (y)	Disease course	Family history	Medication	Agree rTMS	IRLSSG	PSQI	HAM-A	HAM-D
Patients										
1	F	51	6	No			22	7	2	5
2	F	55	27	No			12	4	5	6
3	M	72	5	Yes		Yes	18	11	7	6
4	F	44	10	No			28	13	6	5
5	F	67	4	Yes		Yes	24	13	5	8
6	F	35	7	No			13	4	3	5
7	F	52	34	Yes		Yes	24	13	7	9
8	F	63	35	Yes		Yes	27	15	5	7
9	F	52	4	No		Yes	19	7	5	6
10	M	65	31	Yes	Trastal 50 mg		37	17	14	13
11	F	67	41	No	Madopar 187.5 mg Pramipexole 0.25 mg		29	11	5	8
12	F	54	15	Yes	Pramipexole 0.25 mg		20	5	8	5
13	F	61	39	Yes	Pramipexole 0.5 mg	Yes	28	10	8	7
14	F	51	21	No	Pramipexole 0.25 mg Clonazepam 1 mg		28	13	4	7
15	M	59	4	No	Estazolam 1 mg	Yes	22	12	6	13
Mean ± SD	12 F /3M	56.53 ± 9.75	18.87 ± 14.29				23.40 ± 6.52	10.33 ± 4.05	6.00 ± 2.78	7.33 ± 2.61
Controls										
1	M	62								
2	F	54								
3	M	71								
4	F	50								
5	F	65								
6	F	35								
7	M	71								
8	M	63								
9	M	65								
10	F	69								
11	F	53								
12	F	61								
13	F	52								
14	M	61								
Mean ± SD	8 F/6 M	59.43 ± 9.83								
p Value	0.18[a]	0.43[b]								

F, female; IRLSSG, International Restless Leg Study Group Severity Scale; HAM-D, Hamilton Depression Rating Scale; HAM-A, Hamilton Anxiety Rating Scale; M, male; PSQI, Pittsburgh Sleep Quality Index; RLS, restless legs syndrome; rTMS, repetitive transcranial magnetic stimulation; SD, standard deviation.

[a] *p* Value obtained by two-tailed Pearson χ^2 test, which was used for gender comparison between the idiopathic RLS patients and controls.

[b] *p* Value obtained by a two-sample, two-tailed t-test, which was used for age comparison between the idiopathic RLS patients and controls.