

Repetitive Transcranial Magnetic Stimulation for the Treatment of Restless Legs Syndrome

Yi-Cong Lin^{1,2}, Yang Feng³, Shu-Qin Zhan^{1,2}, Ning Li^{1,2}, Yan Ding^{1,2}, Yue Hou^{1,2}, Li Wang^{1,2}, Hua Lin^{1,2}, Ying Sun^{1,2}, Zhao-Yang Huang^{1,2}, Qing Xue^{1,2}, Yu-Ping Wang^{1,2,4}

¹Department of Neurology, Xuanwu Hospital, Capital Medical University, Beijing 100053, China

²Beijing Key Laboratory of Neuromodulation, Beijing 100053, China

³Department of Neurology, Second Hospital of Hebei Medical University, Shijiazhuang, Hebei 050035, China

⁴Center of Epilepsy, Beijing Institute for Brain Disorders, Laboratory of Brain Disorders, Capital Medical University, Ministry of Science and Technology, Beijing 100069, China

Yi-Cong Lin and Yang Feng contributed equally to this work.

Abstract

Background: Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive technique used to alter cortex excitability that has been proposed as an efficient method for treating brain hyperexcitability or hypoexcitability disorders. The aim of this study was to investigate whether high-frequency rTMS could have any beneficial effects in restless legs syndrome (RLS).

Methods: Fourteen patients with RLS were given high-frequency rTMS (15 Hz, 100% motor threshold) to the leg representation motor cortex area of the frontal lobe for 14 sessions over 18 days. Patients were diagnosed according to the international criteria proposed by the International Restless Legs Syndrome Study Group in 2003. The International RLS Rating Scale (IRLS-RS), Pittsburgh Sleep Quality Index (PSQI), Hamilton Anxiety Scale (HAMA) and Hamilton Depression Scale were used to evaluate the severity of RLS, sleep quality, anxiety and depression, respectively. The scale scores were evaluated at four-time points (baseline, end of the 14th session, and at 1- and 2-month posttreatment). One-way analysis of variance was used to compare scale scores at different time points.

Results: There was significant improvement in the IRLS-RS (from 23.86 ± 5.88 to 11.21 ± 7.23 , $P < 0.05$), PSQI (from 15.00 ± 4.88 to 9.29 ± 3.91 , $P < 0.05$), and HAMA (from 17.93 ± 7.11 to 10.36 ± 7.13 , $P < 0.05$) scale scores at the end of 14th session, with ongoing effects lasting for at least 2 months.

Conclusions: High-frequency rTMS can markedly alleviate the motor system symptoms, sleep disturbances, and anxiety in RLS patients. These results suggest that rTMS might be an option for treating RLS.

Key words: Anxiety; Depression; Restless Legs Syndrome; Sleep; Transcranial Magnetic Stimulation

INTRODUCTION

Restless legs syndrome (RLS) is a sensorimotor disorder characterized by an urge to move the legs that are associated with unpleasant paresthesias. Usually, the symptoms worsen when at rest and at night and are relieved by movement. The etiology of RLS is still unclear. Various studies suggest that genetic component, iron-deficiency, disturbances in the dopaminergic neurotransmitter system and abnormality in spinal conduction pathways are associated with the disorder.^[1] In addition, a malfunction of inhibitory neuronal circuits may also play a role.^[2]

Transcranial magnetic stimulation (TMS), developed in 1985, is a noninvasive technique with the ability to stimulate

neurons in the cerebral cortex through the scalp safely and with minimal discomfort.^[3] Repetitive TMS (rTMS) is a technique that delivers long trains of closely spaced pulses to specific brain areas in order to alter cortical activity and connectivity. Previous studies have suggested that low-frequency rTMS decreases the excitability of the cortex while high-frequency rTMS increases it.^[4,5] Recently, rTMS has been widely applied in the treatment of patients with psychiatric disorders, epilepsy, migraine, chronic pain, and neurodegenerative disorders, including Parkinson's disease (PD),^[6] although its mechanism is not yet well understood. Numerous reports have demonstrated that rTMS of the human primary motor cortex induces the release of dopamine in the putamen, which indicates that rTMS probably modulates striatal dopaminergic neurotransmission.^[7-10] Currently, an increasing number of

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Address for correspondence: Dr. Yu-Ping Wang,

Department of Neurology, Xuanwu Hospital, Capital Medical University,
Beijing 100053, China

E-Mail: wangyuping01@sina.cn

studies have provided support for a link between RLS and PD. Some studies have found that the prevalence of RLS is higher in patients with PD than in the general population.^[11,12] Functional brain imaging studies found a decrease in striatal D2-receptor binding in RLS patients.^[13] In addition, it is known that RLS patients respond favorably to dopaminergic medications. Based on the common mechanism involving disturbances in the dopaminergic neurotransmitter system between RLS and PD, we investigated whether rTMS application to the cortex was beneficial in patients with RLS.

METHODS

Patients

We included fourteen idiopathic RLS patients treated at the sleep clinic of our hospital between 2011 and 2012 that were diagnosed according to the *International Criteria of the International Restless Legs Syndrome Study Group* set in 2003.^[14] The exclusion criteria were as follows: (i) All secondary RLS stemming from a vitamin deficiency, iron-deficiency anemia, pregnancy, diabetes mellitus, severe metabolic disorders, liver dysfunction, or renal disease; (ii) peripheral neuropathy and radiculopathy; (iii) a history of psychiatric disease; (iv) neuropathic pain; (v) leg cramps or epilepsy; (vi) use of a cardiac pacemaker, vagal nerve stimulator, or any metal implants; (vii) other severe medical diseases. Patients were not placed on any new medications, including dopaminergic agonists, psycholeptics, or benzodiazepines; if they were already taking them for at least 4 weeks prior to the initiation of the study, they continued the medicine throughout the study at the prescribed dosage.

All patients provided written informed consent, and the study had the approval of Hospital Ethics Committee.

Repetitive transcranial magnetic stimulation procedure

We administered rTMS at 15 Hz using a Magstim system (Magstim Super Rapid Stimulator, Magstim Company, Whitland, Dyfed, UK) with a figure-eight coil. The stimulation was performed on both hemispheres. One rTMS train consisted of 75 pulses delivered at 15 Hz with an intertrain interval of 10 min. In one session, 600 pulses (8 rTMS trains) were delivered to each hemisphere. One session was performed per day for 5 continuous days and stopped for 2 days. An additional 4 days stimulation was given followed by another 2 days without treatment. Then, another 4 days of stimulation were given. In total, 14 sessions were performed for each patient in our study.

The patients were seated in a comfortable chair, and the coil was positioned at the leg representation in the motor cortex of frontal lobe. The optimal stimulation position for the tibialis anterior muscle was located by stimulating the presumed motor cortex at every 1 cm in a 6-cm². The resting motor threshold (RMT) was defined as the minimal stimulus intensity that produced a motor evoked potential in the relaxed muscle with a peak-to-peak amplitude of >50 mV on $\geq 50\%$ of 10 trials. The stimulation intensity was at 100% RMT.

Assessment

The International RLS Rating Scale (IRLS-RS), Pittsburgh Sleep Quality Index (PSQI), Hamilton Anxiety Scale (HAMA) and Hamilton Depression Scale (HAMD) were used to evaluate the severity of RLS, quality of sleep, and the severity of anxiety and depression, respectively. The assessments were taken at the baseline (prior to stimulation), at end of 14th session, and at 1- and 2-month posttreatment by a trained clinical neurologist.

Statistical analysis

Statistical analysis was performed using SPSS 11.0 (SPSS Inc., Chicago, IL, USA). One-way analysis of variance was used to compare the means of scale scores at different time points. A $P < 0.05$ was considered as statistically significant.

RESULTS

Among 14 patients, there were 4 males and 10 females with a mean age of 59.22 ± 10.10 years and a range of 46–73 years. The duration of RLS in these patients ranged from 5 months to 3 years. The IRLS-RS scores at the four-time points assessed (baseline, end of 14th session, 1- and 2-month posttreatment) are summarized in Table 1. All of the IRLS-RS, PSQI and HAMA scores showed continuous and significant improvement posttreatment compared to baseline. The HAMD scores showed a continuous improvement after treatment but did not differ significantly.

DISCUSSION

Our results indicated a significant improvement in IRLS-RS scores after 14 sessions, from 23.86 ± 5.88 to 11.21 ± 7.23 . This proved the effect of rTMS in treating RLS and that the effect could last for some time (at least 2 months, according to our study) after the stimulation. The mechanism underlying the duration of the effect is unclear. In one study, Khedr *et al.* found that repeated sessions of rTMS could

Table 1: The IRLS-RS, PSQI, HAMA, and HAMD scores in the fourteen idiopathic RLS patients

Time points	IRLS-RS		PSQI scores		HAMA scores		HAMD scores	
	Scores	P value	Scores	P value	Scores	P value	Scores	P value
Baseline	23.86 ± 5.88		15.00 ± 4.88		17.93 ± 7.11		15.43 ± 7.51	
End of 14 th session	11.21 ± 7.23*	0.000	9.29 ± 3.91*	0.000	10.36 ± 7.13*	0.024	8.14 ± 5.85	0.156
1 month post-treatment	11.57 ± 6.84*	0.000	9.07 ± 4.01*	0.003	8.36 ± 6.87*	0.003	7.93 ± 5.78	0.135
2 month post-treatment	14.36 ± 7.71*	0.003	9.64 ± 5.11*	0.009	9.79 ± 7.86*	0.012	7.57 ± 6.51	0.108

IRLS-RS: International RLS Rating Scale; PSQI: Pittsburgh Sleep Quality Index; HAMA: Hamilton Anxiety Scale; HAMD: Hamilton Depression Scale. *Different from 'baseline', $P < 0.05$.

produce prolonged changes in enhanced dopamine function that may be responsible for long-lasting clinical effects.^[15]

After rTMS treatment, PSQI scores decreased from 15.00 ± 4.88 to 9.29 ± 3.91 and persisted at least 2 months after treatment. The long-lasting change in PSQI scores was consistent with the improvement in IRLS-RS scores. Epidemiological and clinical studies have established a close relationship between sleep and mood. Ostacoli *et al.* found RLS patients had significantly higher levels of anxiety and depression.^[16] In our study, RLS patients showed obvious improvements in anxiety, and further improvements occurred in the 2 months after treatment. In addition, the patients' depression improved after treatment, although this change was not statistically significant. It is likely that rTMS improved symptoms of RLS directly rather than its associated symptoms, such as mood disorders, which in turn led to an improvement in symptoms of RLS. Many studies have indicated that RLS is not associated with the use of antidepressants, and some studies have suggested that antidepressants might exacerbate RLS symptoms.^[17-19] In addition, depression did not improve as significantly as the symptoms of RLS in our study. Thus, we believe that rTMS alleviates RLS directly rather than through the treatment of associated symptoms.

A study independently examining the treatment of RLS with rTMS has been published.^[20] Burcu *et al.* found that high-frequency rTMS over the supplementary motor area (SMA) improved IRLS-RS scores significantly after 5 and 10 sessions of stimulation. This result is consistent with ours, although the configuration of stimulation parameters differed, and they did not evaluate sleep quality, anxiety or depression. In Burcu's study, the stimulus frequency was 5 Hz, and the stimulation was centered at points 3 cm anterior to the leg motor area at the sagittal midline. Their parameters were taken from a previous study of PD, in which 5 Hz rTMS was administered over the SMA, resulting in a modest improvement of motor symptoms.^[21] The SMA is important for preparation and execution of voluntary movements. A recent study verified connectivity between the SMA and the primary motor cortex.^[22] Because stimulating either the SMA or the primary motor cortex can alleviate RLS syndrome, we speculate a common effect of rTMS on "upstream" SMA and "downstream" primary motor cortex. The exact mechanism underlying the treatment of RLS with rTMS is complex and not clearly understood. Previous studies have revealed a shortened cortical silent period in the anterior tibialis muscle in patients with RLS, which indicated a disturbed supraspinal inhibition mediated by decreased excitation of cortical inhibitory interneurons, thus leading to the hyperexcitability of spinal pathways.^[2,23] Another probable mechanism involves the release of endogenous dopamine in the striatum, based on single photon emission computed tomography studies. However, a study conducted in Japan suggested that chronic rTMS had a limited effect on the dopaminergic system.^[24] Hence, there may be multiple mechanisms of action involved in modulating symptoms

of RLS. Revealing the exact mechanism is interesting and valuable and should be the subject of future study. In addition, no adverse effects were observed during stimulation or after treatment, and all patients showed good compliance. Thus, 15 Hz rTMS delivered over the leg representation area of motor cortex is a safe treatment for RLS. Medications traditionally used to treat RLS provide dramatic immediate benefits but may augment RLS symptoms over time. Thus, rTMS and medications each possess advantages and provide patients with a variety of treatment options.

However, our study had a limited sample size and no control group, therefore, a large case-control study is necessary to provide more convincing evidence. In addition, an optimized rTMS paradigm should be established. In the future, we plan to compare cortical excitement before and after rTMS treatment using neurophysiological and imaging measurements, such as paired pulse TMS and functional magnetic resonance imaging, to identify the mechanism underlying RLS.

In conclusion, our study proves the utility of rTMS for the treatment of RLS patients despite the study's limited sample size. The clinical symptoms of RLS tended to improve over time following rTMS. In the future, a large case-control study should be performed, and the rTMS protocol should be optimized.

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