The Effects of Neuroplasticity on Major Depression Disorder in rTMS Combined with Antidepressant Treatments

Qinpu He Department of Behavioral Neuroscience Centre College Danville, Kentucky, 40422, USA

Faculty Advisor: Dr. Zhong Zheng

Abstract

Many people suffer from major depression disorders (MMD) but antidepressant treatment doesn't work for 30% of MMD patients. The effects and therapeutic mechanism of repetitive transcranical magnetic stimulation (rTMS) are still unclear. This research studied the effects of treating MMD by rTMS by comparing a group of patients receiving both the antidepressant selective serotonin re-uptake (SSRI) and rTMS treatment with another group receiving. These results show that rTMS with antidepressant treatment can reduce MMD symptoms and therefore keep brain function in dynamic stability. The groups of patients receiving both rTMS treatments and antidepressant have an effective rate of 86.67% after 2 weeks and 72.00% after 10 weeks. The group of patients receiving just antidepressant treatment has an effective rate of 7.14% after 2 weeks and 54.76% after 10 weeks. This research found that rTMS with antidepressant treatment will result in a decrease in depression symptoms and the effective rates of rTMS with antidepressant treatment after 2 and 10 weeks were significantly higher than those of antidepressant treatment. This result suggests that antidepressant combined with rTMS treatment is more effective in treatment. Hence, rTMS can be more extensively used in the treatment of MMD patients.

Key Words: Depression, rTMS, Treatment.

1. Introduction

Major Depression Disorder (MDD) is a mental disorder that is characterized by persistent low mood, low selfesteem and loss of interest in normally enjoyable activities. MDD is pervasive and triggers suicide quickly. A person having a major depressive episode usually exhibits a very low mood, which pervades all aspects of life, and an inability to experience pleasure in activities that were formerly enjoyed. Depressed people may be preoccupied with thoughts and feelings of worthlessness, inappropriate guilt or regret, helplessness, hopelessness, and self-hatred. In severe cases, depressed people may have delusions or hallucinations. It affects approximately 14.8 million American adults, or about 6.7% of the US population who are age 18 and older. In the United States, around 3.4% of people with MDD commit suicide and up to 60% who commit suicide had depression or another mood disorder.

MDD is pervasive but it's hard to treat. There are three major treatments for MDD so far^{1,8}. The first treatment is antidepressant medication. Some important examples of antidepressants are the selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). However, between 30% and 50% of individuals treated with a given antidepressant do not show a response^{2, 5, 7}.

The second prevalent MDD treatment is Psychotherapy or Counseling. Psychotherapy is a therapeutic interaction or treatment contracted between a trained professional and a client, patient, family, couple, or group. It serves to explore the thoughts, feelings and behavior of patients for the purpose of problem solving or achieving higher levels

of functioning. However, the effectiveness of medication for mild or moderate cases is questionable¹².

A minority of MDD patients was treated with electroconvulsive therapy (ECT) ^{13,4,6,9}. ECT is also known as electroshock, which is a standard psychiatric treatment in which seizures are electrically induced in patients to provide relief from psychiatric illnesses. Although a large among of research has been carried out, the exact mechanism of action of ECT remains elusive.

Transcranial magnetic stimulation (TMS) is a noninvasive method to cause depolarization or hyperpolarization in the neurons of the brain. It's a newly invented way to treat MDD and other mental mood disorders^{10, 3}. rTMS causes movement in certain part of the brain without discomforts by using electromagnetic induction. The coils will produce electric currents when the magnetic field around it changes. rTMS helps researchers to study the brain's functioning and interconnections.

While repetitive transcranical magnetic stimulation (rTMS) has already been supported by previous literatures to be effective in treating MDD and has been included into the *Practice Guideline For the Treatment of Patients With Major Depressive Disorder (the Third Edition),* the therapeutic mechanisms of rTMS remains unclear. The purpose of this research was study the effects of treating MMD by rTMS thoroughly by comparing a group of patients receiving both antidepressant and rTMS treatment with another group receiving just antidepressant treatment¹¹. The hypothesis of the present is study was that the group with antidepressant and rTMS treatment would show a higher recovery rate than the other group with just antidepressant treatment.

2. Methodology

2.1 Participants

A total of 159 participants (71 males and 88 females) ranging from 18 to 60 were recruited for the present study. All participants were patients with relapsed MDD after the cessation of antidepressant for more than three months. They were all treated in China Medical School of Sichuan University from 2010 to 2012. All patients were diagnosed as MDD patients with DSM-IV standards for major depression disorders. Although participants had different mood level and mental status at the time of experiment, they all rated \geq 17 on Hamilton Depression Scale (HAMD). Patients with stroke and other severe bodily diseases, patients in encyesis and breast-feeding period were excluded from this research. All participants were notified ahead of the functions and underlying principles of rTMS and its benefits and risks. Informed consent was signed before the study.

2.2 Materials

Selective serotonin reuptake inhibitor (SSRI) was administered to patients in this study. Patients also received Paroxetine, Sertraline Hydrochloride, Citalopram and Fluoxetine as antidepressant medicines in this study and they were monitored to ensure an equal amount of intake of all medicines throughout groups and experimental days. The amount of medicine received by every patient differs according to their respective nature but the influence of these different dosages was negligible because a large number of patients were recruited in this study.

2.3 Apparatus

The Magstim Rapid 2 produced by Magstim Company in England was used as rTMS machine in this study. MEB-9200 evoked potentials machines produced by Nihon Kohden in Japan were adopted to conduct mismatch negative (MMN) and sensory gating potentials (SG-P₅₀) examinations.

2.4 Procedure

A total of 159 patients with MDD randomly divided into two groups: 75 patients in group A (18 males and 57 females) were administrated rTMS treatment for two weeks (15 days), and continued to give antidepressant of selective serotonin reuptake inhibitor (SSRI) regularly. Eighty-four patients in group B (25 males and 59 females) were consistently administered the similar antidepressant. The 24-item Hamilton Depression Scale (HAMD-24), MMN latency, S_1 - P_{50} amplitude, S_2 - P_{50} amplitude and S_2 - P_{50} / S_1 - P_{50} amplitude ratio, and the percentages of

abnormal P_{50} (S₂-P₅₀/S₁-P₅₀ \ge 0.5) were assessed and measured before treatment, at the 2nd and the 10th weekend after treatment in two treatment groups. Meanwhile, 90 cases of normal control group C (28 males and 62 females) were set up. There did not exist any significant differences of demographics among three groups.

Magstim Rapid ² was used to deliver rTMS treatment. The motor threshold (MT) and dorsolateral prefrontal cortex position (DLPFC) were determined in the first treatment. The temperature of the treatment room was control between 16-23 Celsius. Patients were asked to lie down on the bed and received rTMS treatment by "8" shaped coils. MEPs from thenar muscles on hands were recorded. Then rTMS machine were adjusted to make sure at least 5 out of 10 stimulations resulted in MEPs with aptitudes greater than 50 μ V. Then the output stimulation would be MT at that time and 4-5 cm in front of MEPs positions would be DLPFC.

Previous studies constructed the foundations that MDD patients have contrary MCE asymmetry compared to normal people. Their left hemispheres (dominant hemispheres) have lower MCE than normal people while right hemispheres (non-dominant hemispheres) have higher MCE. rTMS with high frequencies (\geq 5Hz) and low frequencies (\leq 1Hz) can increase and decrease MCE, respectively. According to this finding, treating right hemisphere with low frequency rTMS or treating left hemisphere with high frequency would lead to similar antidepressant effects and decrease anxiety likely. Hence, the present study employed 90% MT to stimulate both hemispheres with 1 Hz low frequency (10 impulses per cluster; 10s cluster interval) stimulating right side DLPFC and 20 Hz high frequency (20 impulses per cluster; 20s cluster interval) stimulating left side DLPFC. The total number of stimulations on either side was 800 per day.

Group A received one rTMS treatment per day for six consecutive days and then had a one-day break. A total of 15-day-treatment was administered. MMN and P50 examinations were conducted in this study. For MMN examination, electrodes were applied on Cz and Fz and the ground connection electrode were put on FPz. Oddball mode was used to stimulated patients. The machine released a series of high probability (80%) standard stimulations (1000 Hz, 60 dB) and low probability (20%) deviated stimulations (2000 Hz, 80 dB). The rate of stimulation was 1 Hz and the analysis time was 100 ms/div with an accuracy of 20 μ V/div. Patients were not asked for any reactions and the mismatch negativity wave was obtained by deducting the standard stimulation wave from the deviated stimulation wave. The incubation period of MMN was measured by setting the MMN wave shape from the Fz position. For P₅₀ examination, paired S₁ (conditions) - S₂ (testings) short-interval auditory excitements mode was adopted. The interval between condition and testing was 500 ms and the interval between each pair was 10 s. The analysis time was 30 ms/div with an accuracy of 10 μ V/div. Patients were also allowed for no reactions during this testing. The amplitudes of P₅₀, S₂-P₅₀, S₂-P₅₀/S₁-P₅₀ ratio and the percentage of P₅₀ abnormality (S₂-P₅₀/S₁-P₅₀≥0.5) were recorded. MMN and P₅₀ examinations were conducted before treatment, two weeks and ten weeks after treatments.

3. Results

Group A and B did not differ significantly in their HAMD scores (p > 0.05). Two and ten weeks after treatment, the HAMD-24 scores were reduced remarkably than those before treatment in group A and B (P<0.001), and it in group A was lower than it in group B (P<0.001). The HAMD score of after ten weeks were significantly lower than two week (p<0.001). As can been seen in Table 1, the recovery percentage of group A after two and ten weeks were 86.67% (65/75) and 72.00% (54/75), respectively and those of group B were, respectively, 7.14% (6/84) and 54.76% (46/84).

Group A and B did not differ significantly in their MMN incubation latencies, P_{50} amplitudes, S_2-P_{50} amplitudes, $S_2-P_{50}/S_1-P_{50}/S_1-P_{50}$ ratio and the percentage of P_{50} abnormality $S_2-P_{50}/S_1-P_{50}\ge 0.5$). MMN latencies and S_2-P_{50} amplitudes after treatment in group A were significant shorter and lower than those before treatment in group A and after treatment in group B (*P*<0.05) (except for intergroup comparison of S_2-P_{50} amplitude after treatment 10 weeks). There was not statistically significant S_2-P_{50} / S_1-P_{50} ratio (except for after treatment 2 weeks) and percentage of abnormal P_{50} between group A after treatment and group C (*P*>0.05). There were no statistical significance difference of ERPs between after treatment 2 weeks and 10 weeks in group A (*P*>0.05). There were no statistical differences of ERPs between before and after treatment in group B (*P*>0.05) (see table 2).

Table 1. Comparison of HAMD score between tow treatment groups

	A group (n=75)	B group (n=84)	F	Р
Before Treatment	30.09±9.03	31.05±9.15	0.47	0.51
2 Weeks of Treatment	10.24±3.76 ^{*」+#}	$20.15{\pm}6.48^*$	134.97	0
10 Weeks of Treatment	10.61±5.02 ^{*」} *#	16.07±6.48 [*] ∍*∆	34.64	0

* $P \le 0.001$, vs. before treatmet; # $P \le 0.001$, vs. B group; $\Delta P \le 0.001$, vs. 2 weeks of treatmet in B group

Table 2. Comparison of event related potentials in three groups

Group	Time	n_MMN (ms)	S1-P50(µV)	S2-P50(µV)	S2-P50/ S1-P50	Abnormal P50			
Cases (%)									
A	Before 75	234.89±41.22*	20.73±11.30	10.30±4.41*	$0.65 \pm 0.52^{\#}$	41 (54.67) [#]			
	2 weeks 75	208.05±28.54 [*] ▲ +	18.63±9.61	8.14±3.72 ^{⇔ ▽}	0.57±0.64△	29 (38.67)			
	10 weeks 75	205.89±33.52 [*]	19.67±10.38	$8.08{\pm}3.33^{\diamond}$	0.52±0.37	32 (42.67)			
В	Before 84	231.11±31.14 [*]	18.20±10.20	$10.41 \pm 4.10^{*}$	$0.73 \pm 0.52^{*}$	47 (55.96) [#]			
	2 weeks 84	224.16±29.93*	18.55±9.56	9.80±3.72 [*]	0.63±0.42△	46 (54.76) [#]			
	10 weeks 84	221.57±33.58 [*]	18.16±9.07	9.27±4.85 [#]	0.60±0.43△	43 (51.19)△			
С	90	187.38±31.06	19.34±10.29	7.45±3.98	0.43±0.19	29 (32.22)			

* P < 0.001, # P < 0.01, $\Delta P < 0.05$, vs. control group ; $\Delta P < 0.001$, $\Diamond P < 0.01$, vs. before treatment ; +P < 0.01,

 $\nabla P < 0.05$, vs. 2 weeks of treatment in B group ; $\mathbf{\nabla} P < 0.01$, vs. 10 weeks of treatment in B group

4. Conclusion

rTMS combined with antidepressant therapy was superior to single antidepressant treatment, and marked improved automatic processing and sensory gating of the brain senior functional electrical physiological index. rTMS might induce effects of long-term potentiation/ long-term depression like plasticity on brain, and keep brain function in a dynamic stability and balance. MMN and P_{50} maybe become neuroplasticity index reflecting relevant the brain senior function.

Human brain has automatic processing and controlled processing for the cognizance of experimental stimuli. MMN measures an individual's automatic processing of external stimuli and it reflects the abilities of the brain to process information on early stage. The MMN latencies were normally between 150-200 ms, which was considered by many scholars as caused by internal ERPs. It leaves impressions for high probability events and results in reactions when a novel stimulus was received. Besides, human has sensory gating (SG) to help to minimize the amount of unrelated stimuli that entered the brain, which will help to avoid an overload from an extra amount of external information.

Neurocircuit changes and regroups according to internal manipulations and environmental stimuli, which is defined as neuroplasticity. Long-term potentiation (LTP) is a specific type of neuroplasticity in which postsynaptic potentials (PSPs) are increased. Long-term depression (LTD) refers to the situation when PSPs lengths decrease after low frequency stimulation. These two types of potentiation are considered the most important ways of neuroplasticity that laid the foundations for learning and memorizing. Paired rTMS or other transcranical electric stimulations can alter brain MCE and thus, result in LTP/LTD plasticity.

The present study found that rTMS with medicine combined treatment decrease MMN latency markedly, which was not demonstrated by antidepressant only treatment. This finding implied that rTMS with antidepressant treatment could alter the automatic processing speed of brain, improve the auditory system's capabilities to categorize, encode and record novel stimuli. On the other hand, the abnormality percentage of P_{50} , S_2 - P_{50} / S_1 - P_{50} amplitudes ratio decreased after antidepressant and rTMS combined treatment, which demonstrated strengthened SG abilities of patients after combined treatments.

Previous studies found that the influence of rTMS on neuroplasticity is related to brain-derived neurotropic factor (BDNF) (Brunoni, 2008). Researchers considered the BDNF of neurosystems includes mature BDNF (mBDFNF) and precursor BNDF (proBDNF), with the former related to LTD and the latter related to LTP. High frequency stimulation and low frequency stimulation by rTMS result in effects similar to LTP and LTD.

Although rTMS and medicine combined treatment showed a marked decrease in HAMD scores. The MMN latencies and S_2 - P_{50} / S_1 - P_{50} amplitudes ratio are still higher than that of the control group. Other studies have demonstrated lessened mental disorder characteristics after rTMS treatment but abnormal MMN latencies and P_{50} amplitudes were still persistent. Besides, the recovery rate of combined treatment after ten weeks were significantly lower than after two weeks while the effects of antidepressant treatments increased along with time. Future studies might want to investigate whether the effects of rTMS on MDD stop after a certain amount of time and whether the repeated administration of rTMS is beneficial to patients.

5. Acknowledgement

The author wishes to express her appreciation to the Brown Fellows Program for providing the grant that funded this research. She also expresses her appreciation to faculty research advisor Dr Zhong Zheng for his guidance and hard work throughout this study.

6. References Cited

1. Meguins, Lucas Crociati. "Deep Brain Stimulation for Treatment-Resistant Depression: A State-of-the-Art Review." (2012).

2. Brunoni, André Russowsky, Chei Tung Teng, Claudio Correa, Marta Imamura, Joaquim P. Brasil-Neto, Raphael Boechat, Moacyr Rosa et al. "Neuromodulation approaches for the treatment of major depression: challenges and recommendations from a working group meeting." *Arquivos de neuro-psiquiatria* 68, no. 3 (2010): 433-451.

3. Brunoni, Andre Russowsky, Paulo Sergio Boggio, and Felipe Fregni. "Can the 'yin and yang'BDNF hypothesis be used to predict the effects of rTMS treatment in neuropsychiatry?." *Medical hypotheses* 71, no. 2 (2008): 279-282.

4. Bystritsky, Alexander, Jonas T. Kaplan, Jamie D. Feusner, Lauren E. Kerwin, Mitali Wadekar, Mark Burock, Allan D. Wu, and Marco Lacoboni. "A preliminary study of fMRI-guided rTMS in the treatment of generalized anxiety disorder." *Journal of Clinical Psychiatry* 69, no. 7 (2008): 1092-1098.

5. Pascual-Leone, Alvaro, Catarina Freitas, Lindsay Oberman, Jared C. Horvath, Mark Halko, Mark Eldaief, Shahid Bashir et al. "Characterizing brain cortical plasticity and network dynamics across the age-span in health and disease with TMS-EEG and TMS-fMRI." *Brain topography* 24, no. 3-4 (2011): 302-315.

6. George, Mark S., Eric M. Wassermann, Wendol A. Williams, Ann Callahan, Terence A. Ketter, Peter Basser, Mark Hallett, and Robert M. Post. "Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression." *Neuroreport* 6, no. 14 (1995): 1853-1856.

7. Hasen, Mahfoodh S. "The Use of Electroconvulsive Therapy in the Psychiatric Unit at Ibn Sina Hospital Mosul." *YEMENI JOURNAL FOR MEDICAL SCIENCES* 1, no. 3 (2009).

8. Fitzgerald, Paul B., Kate Hoy, Zafiris J. Daskalakis, and Jayashri Kulkarni. "A randomized trial of the anti - depressant effects of low - and high - frequency transcranial magnetic stimulation in treatment - resistant depression." *Depression and anxiety* 26, no. 3 (2009): 229-234.

9. Klein, Ehud, Isabella Kreinin, Andrei Chistyakov, Danny Koren, Lilly Mecz, Sarah Marmur, Dorit Ben-Shachar, and Moshe Feinsod. "Therapeutic efficacy of right prefrontal slow repetitive transcranial magnetic stimulation in major depression: a double-blind controlled study." *Archives of general psychiatry* 56, no. 4 (1999): 315-320.

10. Lefaucheur, J. P., B. Lucas, F. Andraud, J. Y. Hogrel, F. Bellivier, A. Del Cul, A. Rousseva, M. Leboyer, and M. L. Paillere-Martinot. "Inter-hemispheric asymmetry of motor corticospinal excitability in major depression studied by transcranial magnetic stimulation." *Journal of psychiatric research* 42, no. 5 (2008): 389-398.

11. MARTIN, JOSÉ LUIS R., Manuel J. Barbanoj, Thomas E. Schlaepfer, Elinor Thompson, Víctor Pérez, and Jaime Kulisevsky. "Repetitive transcranial magnetic stimulation for the treatment of depression Systematic review and meta-analysis." *The British Journal of Psychiatry* 182, no. 6 (2003): 480-491.

12. Speer, A. M., B. E. Benson, T. K. Kimbrell, E. M. Wassermann, M. W. Willis, P. Herscovitch, and R. M. Post. "Opposite effects of high and low frequency rTMS on mood in depressed patients: relationship to baseline cerebral activity on PET." *Journal of affective disorders* 115, no. 3 (2009): 386-394.

13. Wang, Yong, Yi-ru Fang, Xing-shi Chen, Jun Chen, Zhi-guo Wu, Cheng-mei Yuan, Z. H. Yi, Wu Hong, Chen Zhang, and Lan Cao. "A follow-up study on features of sensory gating P50 in treatment-resistant depression patients." *Chinese Medical Journal (English Edition)* 122, no. 24 (2009): 2956.