REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (rTMS) A NEW METHOD IN THE TREATMENT OF MOOD DISORDERS

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ABSTRACT

The purpose of the current study to investigate the theoretical foundations, researches and applications of repetitive transcranial magnetic stimulation (rTMS) in the treatment of mood disorders. For this purpose, the data was collected through a library review. The target population of the present study is all published scientific works including research papers, review articles, case reports, dissertations and books which are related to rTMS. The search for sources continued steadily until the final stages of the study and the collected data was analyzed using a qualitative method. Based on the existing literature, rTMS is defined as the induction of an electrical current inside the brain using a magnetic field outside the brain on the skull. The therapeutic application of rTMS includes a wide range of mental diseases (mood disorders, schizophrenia, anxiety disorders, etc.). In spite of safety concerns and possible side effects, many researchers have assumed a promising future for rTMS.

KEYWORDS: Repetitive Transcranial Magnetic Stimulation (rTMS), Mood Disorders

During the several last decades, electrophysiology has contributed much in understanding probe normal functions and existing brain function disorders in pathological conditions. Electrophysiological methods have been broadly used in the field of therapeutic interventions and the results serve to support them every day more than before. With regard to technological advances achieved, modern techniques have acquired a greater share in achieving the goals of therapeutic interventions and fundamental research in various areas such as medical sciences, neurology and psychiatric and psychological interventions and researches. One area, which has witnessed a significant progress in this regard, is perhaps the area of "brain stimulation" and related technologies. Higgins and George (2009) argue that a great volume of research in fundamental and clinical areas is being conducted about the methods of brain stimulation.

Although brain stimulation methods have shown great therapeutic results, their side effects have always been a concern and have stimulated the researchers to search for and develop accurate and less damaging methods. The proponents of brain stimulation treatments have always been looking for less invasive methods. In other words, the researchers have attempted to obtain significant treatment results by focal stimulation of cortex areas of the brain without imposing a vast convulsion (Sakim et al., 2001). These attempts have led to modern brain stimulation methods some of which are Vagus Nerve Stimulation (VNS), Transcranial Electrical Stimulation (TES), Transcranial Alternating Current Stimulation (tACS), Transcranial Direct Current Stimulation (tDCS), High-definition Transcranial Direct Current Stimulation (HD-tDCS), Low Field Magnetic Stimulation (LFMS), Transcranial Random Noise Stimulation (tRNS), Cranial Electric Stimulation (CES), Magnetic Seizure Therapy (MST) and Deep Brain Stimulation (DBS).

One of such new method which has grabbed the attention of researchers in recent years is "Transcranial Magnetic Stimulation (TMS)". TMS was first introduced by Barker, Jalinos and Freeston (1985). To be brief, TMS is the induction of an electrical current to the brain cortex by creating a magnetic field outside the brain and near the skull (Wassermann & Zimmerman, 2012). The therapeutic method based on this technology is called "Repetitive Transcranial Magnetic Stimulation (rTMS)". rTMS is defined as stimulation of the brain in repetitive sessions with the same conditions for the purpose of creating long-term excitation in brain cortex (Wasserman & Lisanby, 2001). In repetitive transcranial magnetic stimulation (rTMS) method the electric activities in the brain are influenced by the magnetic fields. The magnetic field created by rTMS is painless and safely passes through the skin and the skull and creates a current in neurons of the stimulated area. In this type of treatment, many of rTMS factors can change as stimulation parameters. Stimulation parameters are the number of stimulations, stimulation intensity, stimulation frequency, length of intervals between stimulations, the stimulated

Generally, the applications of this modern technology and the number of conducted researches in this regard, both in medicine and fundamental sciences, are growing every day more than before. Hence, conducting a comprehensive review can provide a suitable background for conducting further fundamental and applied researches in this regard. Accordingly, the aim of the present study is to review the theories, conducted researches and applications of rTMS. Therefore, by reviewing the existing literature in this area, it has been attempted to obtain a comprehensive understanding of the theories, conducted researches, applications of repetitive transcranial magnetic stimulation (rTMS) and an insight of its future.

Background of Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) depends on the principle of electromagnetic induction – a process in which electrical energy converts to magnetic energy and vice versa. Historically, it was Faraday who, in 1831, first argued that the relation between electric energy and the magnetic field is reciprocal (Marcolin & Padberg, 2007). In 1896 Arsonal observed a state of dizziness and giddiness by placing a magnetic coil on the head of his subject. Perhaps we can assume his experiment as the first application of magnetic coils as it is today. A very rudimentary form of the latest applications of electromagnetism was first developed by Bier in 1902. For the first time, he could create vibration of the skull by placing electromagnetic coils on the head of depressed patients. Klein stimulated the muscles of a frog by creating a magnetic field in 1959. Another leap forward in the history of magnetic stimulation was the experiment of Beckford and Freming. They could, for the first time, stimulate the nerve cells of human (George & Belmaker, 2007). In 1983, Diaposon and his colleagues stimulated peripheral organs and recorded the first muscular excitatory potential on that basis. Perhaps the first written idea of the applications of models like TMS in neuro-psychological treatments was the simultaneous patenting of Polacek's and Bier's discoveries in Vienna, Austria. They used a magnetic coil over the skull and tried to cure depression and neurosis by passing the vibration through the skull (George & Belmaker, 2007).

In 1910 and 1911 several other researchers performed different forms of brain stimulation (Dunlop, 1911: cited in George & Belmaker, 2007). One weakness of most of the studies at that time was that it was not clarified on what area of the skull the coil had been exactly placed (George et al., 1999: cited in Khomami, 2008). In those years, the capacitors were not capable of producing high intensity or fast frequency stimulations; therefore, the exact mechanisms of the remissions were not clear.

The modern transcranial stimulation started in 1985. At that time, Barker and colleagues made the first modern TMS device in Sheffield, UK (Barker et al., 1985). Barker officially demonstrated the effect of magnetic stimulation on motor cortex in the human brain in 1985. Their laboratory is still operational by continuous developing of its tools and devices. The primitive devices were quite slow when recharging and repeated usages extremely increased the coil temperature.

Technological advances and development of modern magnetic field coils which send the signals directly from the coil are more specific and on this basis, the magnetic pulse could be either sent ceaselessly or as repetitive and continuous attempts. This form of repetitive stimulation is abbreviated as rTMS (Pascual-Leone et al., 1994). The first applications of repetitive transcranial magnetic stimulation were limited to diagnosis of neuro-motor disorders. Some years before, Hatlich and colleagues (1992: cited in Pascual-Leone et al., 1994) introduced the idea that the application of rTMS on cortex area has the same effects as antidepressants. However, using the device on the prefrontal area was not considered in the early practices. In 2002, the medical applications of rTMS were confirmed by the Canadian Association of Health. It is nearly 20 years that this technique is being studied in Canada, US, UK, Germany and Japan. Today, this technique, by having the ability to increase or decrease the magnetic energy on cortical areas, has a broad range of applications in the treatment of various psychological disorders. This method was accepted by the Food and Drug Association of the United States on October 8th, 2008 (Khomami, 2008).

Mechanism of Transcranial Magnetic Stimulation Effect

From the pulse inside the coil to the intensity of the stimulation active in depolarization of the nerve cell, Transcranial magnetic stimulation adopts several laws of
physics. TMS equipment is usually simple and includes a transformer for charging a big capacitor which quickly discharges to create a magnetic field pulse during the stimulation by the coil. The sub-circuit is used to adjust the temperature or the intensity and repetition of the pulse. The maximum voltage is nearly 2000 volts and currents are nearly 10000 Amps. It is necessary to have a high-voltage electronic switch to create a short pulse (nearly 250 microseconds or 1/4000 of a second) which is essential for effective stimulation (Ruth et al., 1991). A high-tension cord is necessary for connecting the coil to effectively transfer the powerful current.

When a cable is charged with electric current, magnetic fields are created around that cable. As it was previously mentioned, according to Faraday's Law, when two coils are place beside each other (with no contact) and one of them is charged with electricity, the very short pulse is transferred to the second coil when the current in the first coil is interrupted. The mechanism of this law is that the magnetic fields created by the electric current in the first coil are transferred to the second coil and when the magnetic field is interrupted, an electric current is created in the second coil. In fact, the second coil is not a necessary factor in this process; i.e. the current can be transferred to any other conductor close to the first coil, whether it is a brain or a coil (Pridemoore, 2007: cited in Reza Koochaksarayi, 2011).

Similarly, in rTMS, the magnetic field created by the first coil is transferred to the second coil (the brain) and stimulates the nerve cells of that area. In other words, when the magnetic fields enter the skull, they create a secondary electric current which depolarizes (changing the electric load) the nerve cells. With the current equipment, we can stimulate up to two centimeters down into the brain. Such equipment can usually stimulate the area between the white matter and the gray matter of the brain. In such a situation, the neural axons transfer the created currents about two centimeters lower than the coil and the electric current which causes the neuro-activities of the cells to change is about 70 mill volts (Ruhn & Ilmonaimi, 2002: cited in Reza Koochaksarayi, 2011).

**Application of Transcranial Magnetic Stimulation in the Treatment of Mood Disorders**

**Depression Disorder**

Since the development of rTMS during the past two decades, most of rTMS application related studies are conducted with relation to depression. These studies include a range of uncontrolled clinical studies to controlled clinical and random ones. The studies, in total, show that therapeutic results of rTMS are promising and yet controversial. The amount of positive results vary greatly from one study to another and some reports on the effectiveness of rTMS have never been repeated again. Most of the studies conducted in this field indicate the effectiveness of this method in the treatment of depression (George & Belmaker, 2007).

In fact, rTMS was used as a therapeutic tool to treat depression for the first time in 1993. Since then, depression has been the most prevalent psychological disease in the treatment of which rTMS was performed on the dorsolateral prefrontal cortex (Wassermann & Lisanby, 2001). In 1995, George and colleagues demonstrated that depression scores significantly drop after the treatment by rTMS. In a study on 56 subjects, Figil et al. (1998) showed that 26 of the patients reported at least a 60% decrease of their scores after five days of treatment with rTMS. In 1999, Triggs and colleagues reported an average 41 percent decrease based on HAMD (Hamilton Depression Rating Scale) in ten of the patients with acute depression after treatment with rTMS.

In their review article, Schutter and Honk (2005) from Helmholtz Research Institute at Utrecht University of New Zealand investigated the effects of rTMS on depression. They argued that depression is the result of the decrease of excitability of the cortex at the left prefrontal area. Therefore, they concluded that it is possible to cause an anti-depression by increasing the excitability on the left prefrontal cortex. Schutter believes that rTMS has introduced a new horizon for treating depression. He considers it effective to mildly apply rTMS on the parietal cortex for the treatment of depression. He states that fast rTMS on the cerebellum is effective for the treatment of depression of various groups. Besides, the safety and commitment of rTMS stimulations on the cortex and cerebellum has always been a concern.

Although in most of the studies a high frequency rTMS has been used on the prefrontal cortex, there is evidence that shows the effectiveness of low frequency rTMS for the treatment of depression (Nisra et al., 2005: cited in Khomami, 2008). In a study in which the patients responded to low frequency rTMS on the left prefrontal cortex, more neural activities were observed at this area.
prior to the treatment compared to normal people (Kimbrell et al., 1999). Decrease of the blood flow at the prefrontal area was observed in the reassessment of the patients 72 hours after the application of rTMS.

As previously mentioned, most of the studies concerning the treatment of depression indicate the effectiveness of rTMS on depression (Cotorier, 2005: cited in Khomami, 2008). The first factor analysis by McNamar et al. in 2001 was consisted of only 5 controlled experiments. In 2001, Holtz-Heimer (cited in Cotorier, 2005) reported 12 controlled studies 11 of which were performed on the dorsolateral prefrontal cortex of the left hemisphere. Table 1 summarizes rTMS experiments from 1993 to 2006.

### Table 1: A summary of experiments for the treatment of depression by rTMS

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>n of samples</th>
<th>Frequency (Hz)</th>
<th>Stimulated area</th>
<th>intensity</th>
<th>coil</th>
<th>n of sessions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haflich et al., 1993</td>
<td>2</td>
<td>0.3</td>
<td>Vortex</td>
<td>105-130%</td>
<td>Circular</td>
<td>10</td>
</tr>
<tr>
<td>George et al., 1995</td>
<td>6</td>
<td>20</td>
<td>DLPFC</td>
<td>80%</td>
<td>Figure-8</td>
<td>5</td>
</tr>
<tr>
<td>Grisaru et al., 1998</td>
<td>10</td>
<td>0.3</td>
<td>Vortex and bilateral forehead</td>
<td>Maximum outlet</td>
<td>Circular 14 cm bore</td>
<td>1</td>
</tr>
<tr>
<td>Katata et al., 1996</td>
<td>7</td>
<td>10</td>
<td>Left &amp; right DLPFC</td>
<td>110%</td>
<td>Figure-8</td>
<td>10</td>
</tr>
<tr>
<td>George et al., 1997</td>
<td>12</td>
<td>20</td>
<td>DLPFC</td>
<td>80%</td>
<td>Figure-8</td>
<td>10</td>
</tr>
<tr>
<td>Opstein, 1998</td>
<td>32</td>
<td>10</td>
<td>DLPFC</td>
<td>110%</td>
<td>Figure-8</td>
<td>5</td>
</tr>
<tr>
<td>Finseed at al., 1998</td>
<td>14</td>
<td>1</td>
<td>Right DLPFC</td>
<td>100%</td>
<td>Circular</td>
<td>10</td>
</tr>
<tr>
<td>Klein, 1999</td>
<td>71</td>
<td>1</td>
<td>DLPFC</td>
<td>1 Tesla</td>
<td>Circular</td>
<td>10</td>
</tr>
<tr>
<td>George, 2000</td>
<td>30</td>
<td>20</td>
<td>DLPFC</td>
<td>100%</td>
<td>Figure-8</td>
<td>10</td>
</tr>
<tr>
<td>Mans, 2001</td>
<td>20</td>
<td>20</td>
<td>DLPFC</td>
<td>80%</td>
<td>Figure-8</td>
<td>5</td>
</tr>
<tr>
<td>Hopner, 2003</td>
<td>30</td>
<td>20</td>
<td>Left &amp; right DLPFC</td>
<td>120%</td>
<td>Figure-8</td>
<td>10</td>
</tr>
<tr>
<td>Hatchman, 2004</td>
<td>48</td>
<td>20+1</td>
<td>Left &amp; right DLPFC</td>
<td>100%</td>
<td>Figure-8</td>
<td>10</td>
</tr>
<tr>
<td>Rumi, 2005</td>
<td>46</td>
<td>5</td>
<td>DLPFC</td>
<td>120%</td>
<td>Figure-8</td>
<td>20</td>
</tr>
<tr>
<td>Fitzgerald, 2006</td>
<td>68</td>
<td>10+1</td>
<td>Left &amp; right DLPFC</td>
<td>110%</td>
<td>Figure-8</td>
<td>30</td>
</tr>
</tbody>
</table>

As it can be seen in table 1, stimulation parameters of the studies differ. In fact, one of the problems that still exist in this area is the indetermination of optimal and equal parameters. In spite of the effectiveness of rTMS in the treatment of depression, performing random tests seems to be necessary due to issues such as small number of samples, non-homogeneity of the control group, non-random selection of the subjects, simultaneous consumption of drugs or other treatments and, finally, non-perseverance of long-term assessments.

In total, by considering the reviewed literature, rTMS technique has a great potential for the treatment of depression and even other types of disorders. However, by considering the findings, it becomes clear that some stimulation parameters and methodologies are determining factors in the effectiveness of rTMS. Such parameters and methodologies could be the source of controversies and contrary results. Anyway, conducting further researches and adopting optimized parameters can help therapeutic specialists and researchers to develop a more equal set of instructions for the treatment of depression (Pirmoradi et al., 2012).

### Mania Disorder

Mania is a severe psychological disorder which often leads to hospitalization and serious problems in family and business. Although there are many drugs available to cure mania, all such treatments need 2-3 week periods for clinical results (Belmaker & Fleischman, 1995). During mania period, it might be required to physically control or tranquillize the patient by benzodiazepine which increases the risks of collapsing, aspiration or uncontrolled behavior. Electroconvulsive therapy for mania is as effective as it is for depression. Since repetitive transcranial magnetic stimulation can have the same characteristics of electroconvulsive therapy (Belmaker & Fleischman, 1995), the researchers have...
used it to see whether it is effective in the treatment of mania. Comparative study of maniac patients and normal participants showed little effectiveness. Thus, some have compared its effect on the left and right prefrontal cortex. The difficulty of the drugless studies on mania is quite well-known. For this reason, some studies were designed to compare the effects of rTMS on the left and right hemispheres along with taking drugs. Considering the quick response of the maniac patients to electroconvulsive therapy, it is assumed that the effect of rTMS is so quick and powerful that, compared to the effects of drugs, it is better observable and measurable.

In a study by Grisaru et al. (1998), the participating patients had syndromes of mania according to DSM-IV. The patients who had the experience of epilepsy, neural surgery, brain trauma, and drug abuse were removed from the study. 16 participating patients were averagely hospitalized for 6-8 days before the study. The patients were assessed four times: 24 hours before rTMS treatment (baseline), three and seven days after the first treatment, and at the end of the study (the 14th day), which was 4 days later than the last treatment. The results of the study showed that rTMS stimulation on the right prefrontal cortex has medical effects. The right area is located in front of the lobe which is reported to have antidepressant effects. Interestingly, lateral right side electroconvulsive therapy did not have any effects on mania in a small number of the subjects. rTMS effects may be complex in psychological treatments because they increase specific patterns of activity stimulation and neural motion, while other parameters could be intervening or preventive (Pascual-Leone et al., 1994). Therefore, more studies on frequencies, intensities, and coil locations are necessary to confirm positive medical effects of rTMS on mania.

The findings of the study of Grisaru et al. which was previously discussed might be the consequences of left rTMS destructive effects on mania. This effect is created together with the preventive effect of monoamine anti-depressant. Therefore, in order to closely examine these results, Kaptzan and colleagues decided to investigate the effectiveness of rTMS on right prefrontal cortex in comparison to pseudo rTMS in mania treatment. 22 patients who were qualified according to DSM-IV participated in this study. None of the subjects had participated in the previous rTMS study. The patients were examined at four stages: 24 hours before the treatment (baseline), three and seven days after the first treatment, and at the end of the study (14th day) which was 4 days after the last treatment. Stimulations were applied by a circular fast coil with a bore of 9 centimeters.

The findings did not support the effectiveness of using rTMS on right prefrontal cortex in the treatment of mania. Combination of the findings of both studies may indicate that the applied TMS on left prefrontal cortex may neutralize the effect of simultaneously used anti-mania drugs. Several factors must be taken into consideration: 16 of 19 patients who participated in the study by Kaptzan and colleagues (2003) had psychotic mania. The effect of rTMS on this group was less than the group in the previous study (by Grisaru et al., 1998). This result is very similar to the difference of rTMS effect on psychotic depression and neurotic depression patients (Grunhaus et al., 2000). The daily dosage of Chlorpromazine in the study of Kaptzan et al. was 490mg for the right rTMS group and 445mg for the pseudo rTMS group, while in the study by Kaptzan and colleagues, it was 240mg for right rTMS and 340mg for left rTMS groups. Therefore, the less dosage for the pseudo group in the study of Kaptzan et al. might be the cause of lesser effectiveness of rTMS.

Michael and Airforth (2000: cited in Kaptzan et al., 2003) applied rTMS on maniac patients at five sessions during the first and second weeks and three sessions during the third and fourth weeks. Two hospitalized bipolar patients who were diagnosed to have mania were treated with fast transcranial magnetic stimulation on the right prefrontal cortex. Eight of the patients received rTMS as a supplement of ineffective (or very little effective) medicinal treatment. After 4 weeks of treatment, rTMS could create relatively stable effects on the decrease of mania symptoms in all patients. A clear causative relation between rTMS and the decrease of mania symptoms cannot be deduced from open and supplementary methods. However, the data are in line with the theory that the application of rTMS on right prefrontal cortex as a supplementary treatment for bipolar maniac patients is safe effective.

Some researchers have warned about the unsafe risks of using pseudo rTMS. According to others, a longer period of treatment, more intensive intervention, high frequencies and the difference of the parameters and the location of the coil can increase the effectiveness of rTMS for mania. It is difficult to test a new treatment method as a supplement of other treatments. Most anti-depressions
do not have any supplementary or additional effects together with other treatments. Thus, it is important that rTMS is used as a single treatment in future for cases of slight mania when there are no moral and practical problems.

**DISCUSSION AND FUTURE PERSPECTIVE**

There is a need for conducting studies which determine whether there are any specific types of diseases which respond well to rTMS. There are some other remaining questions as well such as the period in which the anti-depressant effect of rTMS is stable, and if drugs play any roles in combination with rTMS or solely in acute treatment, following the acute treatment and as a preventive agent. In terms of safety concerns, as the ratio of risk to benefit depends upon personal differences, different operators and usage can differ too. Ultimately, all these issues require the development of a set of universal training instructions and setting credential requisites for rTMS physicians. Who should perform rTMS? How can we make sure that physicians correctly and safely perform rTMS? Currently, there is no comprehensive set of training instructions for rTMS; however it is highly recommended that physicians must be well knowledgeable of brain physiologic principles and rTMS mechanisms, protocols and safety provisions. Thus, it is obvious that there is a need for more rigid rules or at least instructions. (Nejati, 2010). In the next step, if we develop a treatment paradigm which follows such research protocols, some defections will probably appear. Although it is not always possible to interpret and generalize the effects in the populations of normal people to the populations of clinical patients, considering cognitive intervention on the list of the side effects is worth to be discussed (George & Belmaker, 2007).

The basic question is that do rTMS effects last enough to be medically beneficial? There are two answers for this question. First, in some cases if a prolonged treatment is available at some time later, probably a temporary effect will suffice. For instance, if a patient is provided with the implementation of deep or cortex stimulation device, remission of depression in patients resistant to medical treatment will be probably useful. In fact, some authors advocate the application of rTMS on the motor cortex as a non-invasive experiment for testing whether the implementation of an electric cortex stimulator provides constant remission (Lefaucheur, 2006).

The second answer depends on our assumption of obtaining a medical result with rTMS. In a simple "remedial" model, it is assumed that rTMS corrects the unbalance of the function created by the patient. In this model, if the effects are temporary, the unbalance returns and the symptoms recrudesce. In such a situation, rTMS should create permanent effects in the brain circuit for any effective treatment. Currently there is no evidence that such a thing can happen: in fact, in that case, the use of rTMS on normal people would have been morally wrong. The lasting period of the effect is not the only "remedial" problem. Contrary to a good medicine which has a limited number of pharmaceutical goals, rTMS is famous for creating a blend of stimulating and preventive effects. Therefore, it is not illogical to expect rTMS to remedy the lost function like dopamine-therapy in Parkinson. rTMS cannot have such a characteristic unless there are specific electro physiologic conditions (Miniosi et al., 2005: cited in Lefaucheur et al., 2006).

If we adjust the model in such a way that it is turned into an "interactional" model, then we can give a more positive answer. Such a model does not rely on the notion that rTMS alone can remedy specific functions. Instead, it suggests that rTMS can help the brain to remedy itself. This concept is adopted from the background of apoplexy in which it is accepted that some functional achievements which are regained after the apoplexy have remained due to the reorganization or the brain in normal routes which can compensate for lost functions of other locations to some extent. In this model, some types of rTMS are perhaps ideal methods by which the natural adaptation to the damage or chronic illness increases. In fact, many of rTMS applications have implicitly assumed an "interactional" model for the explanation of stable effects on symptoms. Unfortunately, this logic has been poorly adopted in some studies. Many of the studies are conducted in a small scale and only at one center which makes it difficult to evaluate them. Yet, there are many experiments of rTMS on depression. Reviewing the background of such attempts may reveal the problems of the quick introduction of a new method like rTMS in clinical functions (Martin et al., 2003).

rTMS treatment can be probably organized with respect to the results of the scans at some time in future. Some areas of the cortex which are beneath and over the active areas may be treated in a different way. Clinical studies which benefit from more intensity, increased number of pulses in each session and increased number of...
sessions may result in better medical outcomes (Post et al., 1997).

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