

Repetitive Transcranial Magnetic Stimulation for Clinical Applications in Neurological and Psychiatric Disorders: An Overview

Nörolojik ve Psikiyatrik Bozukluklarda Klinik Uygulamalar için Transkraniyal Manyetik Uyarım: Genel Bir Bakış

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Abstract

Neurological and psychiatric disorders are characterized by several disabling symptoms for which effective, mechanism-based treatments remain elusive. Consequently, more advanced non-invasive therapeutic methods are required. A method that may modulate brain activity and be viable for use in clinical practice is repetitive transcranial magnetic stimulation (rTMS). It is a non-invasive procedure whereby a pulsed magnetic field stimulates electrical activity in the brain. Here, we focus on the basic foundation of rTMS, the main stimulation parameters, the factors that influence individual responses to rTMS and the experimental advances of rTMS that may become a viable clinical application to treat neurological and psychiatric disorders. The findings showed that rTMS can improve some symptoms associated with these conditions and might be useful for promoting cortical plasticity in patients with neurological and psychiatric disorders. However, these changes are transient and it is premature to propose these applications as realistic therapeutic options, even though the rTMS technique has been evidenced as a potential modulator of sensorimotor integration and neuroplasticity. Functional imaging of the region of interest could highlight the capacity of rTMS to bring about plastic changes of the cortical circuitry and hint at future novel clinical interventions. Thus, we recommend that further studies clearly determine the role of rTMS in the treatment of these conditions. Finally, we must remember that however exciting the neurobiological mechanisms might be, the clinical usefulness of rTMS will be determined by its ability to provide patients with neurological and psychiatric disorders with safe, long-lasting and substantial improvements in quality of life.

Key Words: Brain, cortical activity, neuroplasticity, repetitive transcranial magnetic stimulation, sensorimotor integration

Özet

Birkaç engelleyici belirti ile karakterize nörolojik ve psikiyatrik bozukluklar etkili, mekanizmaya dayalı tedavilerden kaçabilir. Nihayetinde daha gelişmiş non-invaziv tedavi yöntemleri gereklidir. Beyin aktivitesini modüle edebilecek ve klinik uygulamada kullanım için uygun olan bir yöntem, tekrarlayan transkraniyal manyetik stimülasyon (rTMS)'dur. Bu, darbeli manyetik alan sayesinde beyindeki elektriksel aktiviteleri uyaran non-invaziv bir işlemdir. Burada, rTMS temeli, ana stimülasyon parametreleri, bireysel yanıtları etkileyen faktörler ve nörolojik ve psikiyatrik bozuklukların tedavisinde uygun bir klinik uygulama olabilecek rTMS'da deneysel gelişmeler üzerine odaklanılmıştır. Bulgular rTMS'un bu koşullar ile ilgili bazı belirtileri düzeltileceği ve nörolojik ve psikiyatrik bozukluğu olan hastalarda kortikal plastisiteyi artırmak için yararlı olabileceğini göstermektedir. Ancak, bu değişiklikler geçicidir ve rTMS tekniği potansiyel bir sensorimotor entegrasyon ve nöroplastisite modülatörü olarak kanıtlanmış olsa bile, gerçekçi tedavi seçenekleri olarak bu uygulamaları önermek için henüz erkendir. İlgili bölgenin fonksiyonel görüntülemesinin yapılması rTMS'un kortikal devrelerde plastik değişiklikler meydana getirme kapasitesini vurgulayarak gelecekteki yeni klinik müdahaleler için ipucu olabilecektir. Böylece, daha ileri çalışmalara açık bir şekilde bu koşulların tedavisinde rTMS'un rolünü araştırmayı öneririz. Son olarak, uyarıcı nörobiyolojik mekanizmaların olması gerektiği gibi, rTMS klinik yararlılığını nörolojik ve psikiyatrik bozukluğu olan hastaların yaşam kalitesinde, güvenli, uzun ömürlü ve esaslı gelişmeler sağlama yeteneği ile belirleneceğini unutmamalıyız.

Anahtar Kelimeler: Beyin, kortikal aktivite, nöroplastisite, tekrarlayan transkraniyal manyetik stimülasyon, sensorimotor entegrasyon

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Introduction

Thirty-one years ago, Merton and Morton built a high-voltage electrical stimulator that was capable of activating muscle directly rather than through the small nerve branches. In addition, Merton taught that the electrical stimulator, called Transcranial Electrical Stimulation (TES), would also be able to stimulate the Motor Cortex (MC) of the human brain noninvasively, i.e., through the intact scalp. They used brief, high-voltage electric shocks to activate the MC and produce a relatively synchronous muscle response, the Motor-Evoked Potential (MEP). Regardless of its many purposes, TES is painful due to its activation of pain fibers in the scalp [1-3]. In line with this, five years later, Barker *et al.* [4] showed that both nerve and brain could be stimulated using Transcranial Magnetic Stimulation (TMS) with little or no pain [3].

TMS is now widely used as a research tool to study aspects of human brain physiology, including motor function, vision, language and the pathophysiology of brain disorders. It may also be useful as a therapeutic tool, particularly in neuropsychiatry [5-7]. Depending on the stimulation parameters used, TMS can excite or inhibit the brain, allowing the functional mapping of cortical regions and the creation of transient functional lesions. Since its introduction as a non-invasive method of stimulating the human brain, TMS in its repetitive form (rTMS) can modulate cortical excitability beyond the period of stimulation itself [3, 8]. Depending on essential stimulation frequency parameters on the number of trains of stimuli delivered, rTMS can produce lasting up- or down-regulation of the corticospinal system [3].

TMS is based on Faraday's law of electromagnetic induction, by which electrical activity in the brain tissue can be influenced by the magnetic field, thereby inducing electrical current that depolarizes neurons [2, 9]. The application of rTMS generates clear effects on a range of measures of brain function and has become an important research tool due to its potential application as a clinical treatment for a variety of neurological and psychiatric disorders, for instance, depression [2, 10-11].

Within this context, the use of rTMS is considered a brain-system-based neuromodulation treatment because it directly targets the neural circuitry of the disorders. rTMS alters or modulates the function of the neural circuitry in the brain that is believed to be disorganized in certain disorders [12-13]. In fact, there is now a growing interest in the research of new treatment for neurological and psychiatric disorders; however, the main focus of the possible therapeutic effects of rTMS remains in the domain of depression [14]. Within this context, the current review paper aims to present basic concepts of TMS, sham-rTMS and stimulation parameters, which influence the individual response to rTMS, and to pro-

vide information on the current research and main findings related to the potential therapeutic effects of rTMS on neurological and psychiatric disorders, such as stroke, Parkinson's disease, anxiety disorders, depression and schizophrenia.

Transcranial Magnetic Stimulation (TMS):

Basic Foundations

TMS have several relevant foundations that must be highlighted to provide a better understanding of its operation. In this section, we will present the main terminology of TMS that has been studied to date. TMS was originally introduced by Anthony Barker *et al.* [4] as non-invasive focal brain stimulation and safe and painless way to study the CNS, more specifically, to activate human motor cortex and assess the human central motor pathways [15].

The main concept of TMS relies on Faraday's law of electromagnetic induction, in which an electrical current is applied over the scalp through a magnetic coil. It involves placing a small coil of wire on the scalp and passing a powerful and rapidly changing current through it. This produces a magnetic field that passes unimpeded and relatively painlessly through the tissues of the head. The TMS equipment consists of a stimulator, which generates brief pulses of strong electrical currents whose frequency and intensity can be varied, and a stimulation coil connected to the stimulator [16]. The TMS coil is typically round or figure-eight (butterfly) in shape; the latter produces a stronger and more focal field than the circular coil. Progress on the technical aspects of TMS devices soon made it possible to deliver multiple pulses within a short time period, i.e., rTMS. Stimulation is delivered in trains that last several seconds, followed by inter-train intervals. The magnetic field (1.5-2.5 T) generated at the coil passes unimpeded through the scalp and skull, inducing a rapid change of current through the underlying tissue that depolarizes neurons, and generates action potentials [3, 17-19].

The maximal field strength generated by commercially available stimulators is in the 2 T range, and these stimulators are able to activate cortical neurons at a depth of 1.5-2 cm beneath the scalp. The precise effect of the stimulation on neuronal activity remains unclear. It is expected that the magnetic stimulus (duration of 100 ms) synchronously excites a population of neurons, inducing rapid changes in the firing rates of certain neural networks during only a few milliseconds [7]. Moreover, this process generally lasts between 20 and 200 ms depending on stimulus intensity. The area of stimulation depends not only on coil geometry but also on stimulation intensity [20]; however, another parameter that influences rTMS effects is likely the stimulation frequency.

TMS in its repetitive form (rTMS) can modulate cortical excitability beyond the period of stimulation itself, giving rise to its potential application as a clinical treatment for a variety

of neurological and psychiatric disorders, for instance, anxiety disorders [8, 21]. rTMS can be classified as "high-frequency rTMS" (>1 Hz) or "low-frequency rTMS" (<1 Hz). Although the response to rTMS can vary across individuals [22], high-frequency rTMS seems to facilitate cortical excitability, whereas low-frequency rTMS can suppress this excitability on the motor cortex [23-24]. Recently, a novel pattern of rTMS named Theta-Burst Stimulation (TBS) was developed to produce changes in the human cerebral cortex excitability [25]. The main advantage of the TBS paradigm compared with conventional rTMS protocols is that a shorter period (between 20 and 190 s) of subthreshold stimulation causes changes in cortical excitability that outlast the time of stimulation for at least 15-20 min. Huang et al. [25] proposed a TBS protocol consisting of bursts of 3 pulses given at 50 Hz repeated every 200 ms (5 Hz) to mimic the coupling of theta and gamma rhythms in the brain. Two main modalities of TBS have been tested. Intermittent TBS (iTBS) induces the facilitation of motor cortical excitability, whereas continuous TBS (cTBS) leads to inhibition for 15-30 min after application [25, 26].

Motor cortical excitability is characterized in surface electromyographic recordings considering Motor Evoked Potentials (MEPs) amplitude. The most common value is the resting Motor Threshold (rMT), which is measured with relaxed muscles. It is defined as the minimum amount of energy (i.e., intensity of stimulation) needed to induce a MEP of 50 microvolts in a hand muscle in at least 5 out of 10 consecutive trials [27]. rMT is also used to establish the individual intensity of stimulation, typically described as a percentage of the device's available output [28].

Another criterion to identify the hot spot is the image-guided frameless Stereotaxic Neuronavigation System (SNS). SNS uses the subject's individual MRI for navigation *via* a subject-image co-registration procedure based on facial/cranial landmarks. Although the system's precision has technical limitations, the quality of the MRI investigation and exact co-registration, the spatial deviations have been shown to lie within the millimeter range [29]. Moreover, other rTMS parameters must be taken into account in any type of research, such as the pulse width, inter-train interval (time between trains of stimulation), number of trains per session and duration of the session [30].

Sham-rTMS and Stimulation Parameters: the Key Elements

With respect to rTMS methodology, important considerations must be taken into account to optimize the clinical effects of rTMS. These considerations are the stimulation parameters, e.g., pulse width, number of stimulation sessions, intensity, site of stimulation and frequency [31]. For instance, lower frequencies of rTMS, in the 1 Hz range, can suppress the

excitability of the motor cortex, whereas 20 Hz stimulation trains seem to lead to a temporary increase in cortical excitability [32]. Although these effects vary among individuals, the effect of low-frequency rTMS is robust and long-lasting and can be applied to the motor cortex and other cortical regions to study brain-behavior relations. The mechanisms by which cortical activation occurs are not entirely clear, although some authors suggest that a transient increase in the efficacy of excitatory synapses may play a role. Higher frequencies are achieved because a bipolar stimulus is shorter than a unipolar stimulus and requires less energy to produce neuronal excitation [14].

Perhaps, the most important issue in the TMS research regarding the design of randomized, sham-controlled clinical trials is the use of appropriate control conditions that provide a reliable blinding of patients and investigators [33], such as the most common strategy used, sham stimulation (sham-rTMS) [34]. Careful consideration of cortical targets seems to be critical and might need to be individualized for each patient and underlying pathology. Predictions with regard to the efficacy of clinical effects of rTMS are hampered due to the relative paucity of parametric studies performed on these variables. Moreover, individualizing stimulation parameters, taking into account the underlying pathophysiology and the stimulation settings by online physiological and neuroimaging measures, seem to be a crucial procedure to adopt [33, 34].

Factors Influencing the Individual Response to rTMS

In the last decade, genetic factors in humans have been a crucial topic of discussion in clinical research. The main hypothesis is that common genetic variants might contribute to genetic risk for some diseases and may compromise the subject's response to TMS [35, 36]. We can speculate that a profound knowledge of genetic variants may help to predict whether participants will respond to rTMS and the direction in which the modulation will take place. The Brain Derived Neurotrophic Factor (BDNF) gene has been related to the individual response to rTMS. The BDNF gene has 13 exons and encodes a precursor peptide (pro-BDNF), which in turn is cleaved to form the mature protein. A Single Nucleotide Polymorphism (SNP) located at nucleotide 196 (guanine (G)/ Adenosine (A)) has been identified. The result is an amino acid substitution Valine (Val)-to-Methionine (Met) at codon 66, and it has been hypothesized that SNP located in the pro-BDNF alters intracellular processing and secretion of BDNF [37]. In healthy subjects, it has been related to mild memory impairments, reduction in hippocampal and frontal cortical areas and some personality traits [37]. This Val66Met polymorphism could also be related to psychiatric disorders such as depression and risk of schizophrenia and to the pathogenesis of some neurodegenerative diseases, i.e., Alzheimer's

Disease (AD), Parkinson's Disease (PD) and Amyotrophic Lateral Sclerosis (ALS) [37].

The strong evidence of a functional role for this BDNF common polymorphism and its implication in LTP process yielded to analyze whether a BDNF genotype influences the response to TMS delivered over M1. Little is known regarding this topic. The first investigation showed that the facilitation following the performance of sensorimotor integration tasks, reflected as an increase in the amplitude of cMAPs, was more pronounced in Val/Val polymorphism carriers compared to Val/Met or Met/Met carriers [36]. Other study explored the inhibitory effect of the cTBS protocol in healthy carriers of different polymorphisms of the BDNF gene. The findings suggested that Val/Met or Met/Met (Non-Val/Val) carriers have a reduced response to cTBS compared to subjects with Val66Val polymorphism [35]. In addition to genetic variations, another factor that seems to influence the individual response to TMS is the physiological state of neurons at the time of stimulation. Synaptic plasticity can be modulated by prior synaptic activity. The direction and degree of modulation seem to depend on the previous state of the network. This type of plasticity is called metaplasticity [38, 39]. For example, external stimulation that activates the resting network could decrease the same network if it was not at rest at the moment of stimulation. This finding has been observed in animal models and related to the NMDA receptor activation, Ca_v2 influx, CaM, CaMKII and to modifications of inhibition of GABA release [40].

The phenomenon of metaplasticity has been demonstrated by applying rTMS at cortical regions that have previously been modulated by means of cathodal or anodal transcranial direct current stimulation [41]. One minute of muscular contraction of the Abductor Pollicis Brevis (APB) during TBS over M1 suppressed the effect of the cTBS and iTBS effect on the cMAPs amplitude. When the contraction was held immediately after TBS, it enhanced the facilitatory effect of iTBS and reversed the usual inhibitory effect of cTBS into facilitation. In a second study, the application of 300 pulses of cTBS facilitated cMAPs amplitude, whereas the same train of stimulation preceded by voluntary contraction of 5 min or 600 pulses of cTBS with the muscle at rest decreased it. The results suggest that 300 pulses of cTBS may have a similar mechanism as iTBS and may prime neuronal elements to undergo inhibition by the late cTBS with 600 pulses. Similarly, the change in the TBS effects before or after a muscular contraction provides evidence for metaplasticity of corticospinal excitability in the human M1. These findings must be considered when applying TBS in clinical trials.

rTMS to Treat Neurological and Psychiatric Disorders

Long-lasting influences on the brain depend on changes in synaptic strength, such as alterations in dendritic spines.

Because these anatomical changes may result secondarily in extended changes in synaptic strength, the function of rTMS is to alter synaptic strength. Such an effect has been observed both in neurological and psychiatric disorders; however, it is not limited only to motor areas [14, 32, 42]. Some studies demonstrate these effects in areas outside of the motor cortex, being associated with assessable behavioral changes [3, 5]. This finding raises the possibility of therapeutic applications of rTMS to alter or modulate the function of the neural circuitry in the brain that is believed to be disorganized in certain disorders. rTMS is considered a brain-system-based neuromodulation treatment due to its focus on directly targeting the neural circuitry of the disorders, shifting the perspective of treatment from changing the neurochemistry within the synapse [14, 32, 43]. Therefore, in this section, we will present the main findings related to the potential therapeutic effects of rTMS in neurological and psychiatric disorders (Tables 1 and 2).

Parkinson's Disease

Augmented evidence of the involvement of the sensory system in Parkinson's disease pathophysiology is crucial to consider the possible contribution of changes in neuroplasticity, i.e., the capacity to exploit sensory information accurately to assist neural networks responsible for an appropriate movement execution [44-48]. In line with this, the use of rTMS as a therapeutic tool for these deficits of Parkinson's disease would require repetitive and frequent use to be effective. rTMS has the potential to fulfill an adjunctive treatment role in rehabilitation of Parkinson's disease by a rational and selective modulation of symptoms and their underlying neuro-pathophysiology on an individual basis [49]. In addition, rTMS avoids both complications regarding DBS surgery and side effects of systematic use of medications. The pathophysiological rationale is applying rTMS over selected cortical regions to modulate the specific cortical-subcortical networks that may be responsible for a given subset of symptoms. Thus, rTMS could modulate cortical excitability, underlying adaptive and maladaptive plasticity [50]. Within this context, there are two rationales for the use of this method in Parkinson's disease. The first rationale is its capacity to increase cortical excitability to thalamocortical drive, which is understood to be lacking in this disease. The second rationale is its capacity to modify catecholamine metabolism subcortically through cortical stimulation [51].

However, there is no consensus concerning whether rTMS has any clinical effects in Parkinson's disease sensorimotor functions. The first study to report the clinical effects of rTMS in Parkinson's disease applied 5Hz-rTMS administered at 90% rMT over the primary Motor cortex (M1). Effects on choice Reaction Time (CRT), Movement Time (MT) and Error Rate (ER)

Table 1. Summary of open and controlled studies of rTMS and its effects on neurological disorders

Study	Design	N	rTMS Protocol	Efficacy
Pascual-Leone et al. 1994	RCT 4 sessions on separate days	6 "on drug"	M1-R or L 5Hz at 90% rMT Sham-rTMS	Significant enhancement of reaction time and movement time was found in favor of 5Hz-rTMS compared to sham-rTMS.*
Gabra et al. 1999	Cross-over 4 sessions on separate days	5 "on drug" and 6 "off drug"	M1-R or L 5Hz at 80 to 85% rMT Sham-rTMS	No beneficial effect of 5Hz-rTMS was found compared to sham-rTMS. No significant difference was found in any group separately.
Lefaucheur et al. 2004	RCT 3 sessions (1 per week for 3 week)	12 "on drug"	M1-L 0.5Hz at 80 % rMT M1-L 10Hz at 80 % rMT Sham-rTMS	Significant decrease in bradykinesia and rigidity contralaterally after 10Hz-rTMS and significant reduction in rigidity bilaterally and improvement in walking after 1Hz-rTMS.* However, no significant difference was found between real-rTMS and sham-rTMS.
Khedr et al., 2003	RCT 10 sessions in consecutive Days	36 "off drug"	M1-bilaterally 5Hz at 120% rMT Sham-rTMS	Significant long-term improvement (1 month) in total motor functions (UPDRS), walking speed and self-assessment was found after one month with 5Hz-rTMS compared to sham-rTMS.*
Koch et al. 2005	Cross-over 4 sessions in separate days	8 "on drug"	SMA-bilaterally 1Hz at 90% rMT SMA-bilaterally 5Hz at 110% rMT Mid-parietal 1Hz at 90% rMT Sham-rTMS	Significant reduction of drug-induced dyskinesia after 1Hz-rTMS compared to sham-rTMS and midparietal-rTMS.*
Hamada et al. 2009	RCT 8 sessions (once a week for 8 weeks)	98 "on drug"	SMA-bilaterally 5 Hz at 110% aMT Sham-rTMS	Significant improvement in bradykinesia was found after 5Hz-rTMS compared to sham-rTMS.* The effects of rTMS lasted for at least 2 weeks after the end of the treatment.
Lomarev et al. 2006	RCT 8 sessions (2 per week for 4 weeks)	18 "off drug"	M1- and DLPFC-bilaterally 25 Hz at 100% rMT Sham-rTMS	Significant improvement in gait and reduction in bradykinesia of upper limb were found after 25Hz-rTMS compared to sham rTMS, lasting for at least 1 month after treatment ended.*
Khedr et al. 2006	RCT 6 consecutive sessions	55 "off drug"	M1-bilaterally 25 Hz at 100% rMT – Early PD M1-bilaterally 25 Hz at 100% rMT – Advanced PD M1-bilaterally 10 Hz at 100% rMT Mid-occipital 25 Hz at 100% rMT	Significant improvement in total motor functions (UPDRS), walking speed and keytapping after M1-bilaterally 10 and 25 Hz rTMS compared to occipital 25 Hz rTMS in both PD groups.* The effect at 10 Hz was less significant than that at 25 Hz rTMS. The effect was maintained for 1 month after the treatment.
Khedr et al. 2007	Open 6 consecutive sessions	20 "off drug" 100% rMT	M1-bilaterally 25Hz at	Significant improvements in total motor functions (UPDRS) and in serum dopamine level were found after 25 Hz rTMS. *Moreover, a significant correlation between serum dopamine level and motor functions was found before and after treatment.

Filipovic et al. 2009	Cross-over 4 consecutive sessions	10 "on drug"	M1-L or R 1 Hz at 90 % rMT Sham-rTMS	No significant differences were found between 1 Hz rTMS and sham-rTMS. However, when compared to the baseline, a small but significant reduction in dyskinesia was found in favor of 1Hz-rTMS.*
Filipovic et al. 2010	Cross-over 4 consecutive sessions	10 "on drug"	M1-L or R 1 Hz at 90 % rMT Sham-rTMS	No significant differences were found in favor of 1Hz-rTMS compared to sham-rTMS. No significant difference was found in any group separately.
Stroke				
Liepert et al. 2007	Cross-over 1 session	12 right-handed	cM1 1 Hz at 90 % rMT Sham-rTMS	Significant improvement in NHPT results was found in favor of 1Hz-rTMS compared to sham-rTMS.* However, no significant difference was found in grip strength in the affected hand or in the unaffected hand.
Dafotakis et al., 2008	Cross-over 1 session	12 right-handed	cM1 1 Hz at 100 % rMT Sham-rTMS	Compared to baseline, 1Hz rTMS applied over the uninjured M1, excluding the vertex, enhanced the efficiency and timing of grasping and lifting with the injured hand.*
Di Lazzaro et al. 2008	RCT 1 session	12 right-handed	iM1 iTBS at 80% aMT cM1 cTBS at 80% aMT Sham-TBS	Compared to sham-TBS, both facilitatory TBS in the iM1 and inhibitory TBS in the cM1 generated a significant increase in the amplitude of MEPs derived from stimulation of the damaged hemisphere.*
*Significance level at ≤ 0.05 aMT: active Motor Threshold; cM1: contralesional M1; cTBS: continuous Theta Burst Stimulation; DLPFC: dorso lateral prefrontal cortex; Hz: Hertz; iM1: ipsilesional M1; iTBS: intermittent Theta Burst Stimulation; L: left; MEP: Motor Evoked Potential; MT: motor threshold; NHPT: Nine Hole Peg Test; R: right; RCT: randomized clinical trial; rMT: resting Motor Threshold; rTMS: repetitive transcranial magnetic stimulation; SMA: supplementary motor area; TBS: Theta Burst Stimulation; UPDRS: Unified Parkinson's disease Rating Scale				

in a serial reaction-time task were measured in 6 medicated patients compared to 10 age-matched healthy controls. rTMS significantly reduced the cRT and MT without affecting ER [24].

On the other hand, the experiment of Ghabra *et al.* [52] showed opposite results. They compared the effects of 5Hz-rTMS to sham-rTMS over cM1 in 11 unmedicated similar patients and found no beneficial effect on grooved pegboard test performance during or after stimulation. The stimulation at 90% rMT catastrophically disrupted sensorimotor functions in most of the patients. This phenomenon has been noted by others and associated with the cerebellar tremor. It was found that decreasing the stimulation intensity removed the tremor, but did not improve the task performance [53].

The study of Lefaucheur *et al.* [54] compared low- (0.5Hz) and high-frequencies (10 Hz-rTMS) to sham-rTMS. rTMS was applied over M1 at 80% MT and enhanced numerous aspects of motor performance. Moreover, 10Hz-rTMS decreased rigidity and bradykinesia in the upper limb contralateral to the

stimulation, whereas 0.5 Hz-rTMS reduced upper limb rigidity bilaterally and improved walking. However, these changes lasted only minutes. A more substantial and long-lasting effect of rTMS therapy appears to be produced by repeated application over a period of days [54]. Within this context, 36 unmedicated PD patients were randomized to one of the following two groups: 5Hz-rTMS (once a day to the M1 bilaterally for 10 consecutive days) and sham-rTMS. The former enhanced all motor sections of the UPDRS, walking speed and self-assessment scale after the sessions ended, and the benefit lasted at least one month [55].

With regard to neural mechanisms and circuitry involved in L-DOPA-induced dyskinesia, Koch *et al.* [56] used rTMS over the SMA in a group of advanced PD patients to investigate whether modulation of SMA excitability results in a modification of a dyskinetic state induced by continuous apomorphine infusion. One session of 1Hz-rTMS administered at 90% rMT for 15 min (900 pulses) markedly reduced drug-induced

Table 2. Summary of open and controlled studies of rTMS and its effects on psychiatric disorders

Study	Design	N	rTMS Protocol	Efficacy
OCD				
Greenberg et al. 1998	Open study 1 session	12	PFC-R 20Hz of 80%MT PFC-L 20Hz of 80%MT Occipital 20Hz 80%MT	Reduction in OCD symptoms only with right-sided treatment.*
Sachdev et al. 2001	Open study 10 sessions (5 days per week for 2 weeks)	12	PFC-R 10Hz of 110%MT PFC-L 10Hz of 110%MT	Both groups showed a significant reduction in OCD symptoms.* However, no significant difference was noted between groups.
Alonso et al. 2001	RCT 18 sessions (3 days per week for 6 weeks)	18	DLPFC-R 1Hz of 110%MT Sham-rTMS	Slight reduction in OCD symptoms in rTMS group.* However, no significant difference was noted between groups.
Mantovani et al. 2006	Open study 10 sessions (5 days per week for 2 weeks)	10	SMA-bilaterally 1Hz of 100% MT	Significant reduction in OCD symptoms.*
Prasko et al. 2006	RCT 10 sessions (5 days per week for 2 weeks)	30	DLPFC-L 1Hz of 110%MT Sham-rTMS	Both groups showed a significant reduction in anxiety.* However, no significant difference was found between groups.
Sachdev et al. 2007	RCT 10 sessions (5 days per week for 2 weeks)	18	DLPFC-L 10Hz of 110% MT Sham-rTMS	No significant difference was found between groups. However, after comparison, all subjects who received rTMS showed a significant reduction in OCD symptoms.
Kang et al. 2009	RCT 10 sessions (5 days per week for 2 weeks)	20	DLPFC-R 1 Hz of 110%MT SMA-bilaterally 1Hz of 100% MT Sham-rTMS	No significant difference was found in both groups and between groups.
Ruffini et al. 2009	RCT 15 sessions (5 days per week for 3 weeks)	23	OFC-L 1Hz of 80% MT Sham-rTMS	Significant reduction in OCD symptoms in favor of rTMS compared to sham-rTMS.* However, no significant reduction in anxiety and depression symptoms was found between groups.
Mantovani et al. 2010	RCT 20 sessions (5 days per week for 4 weeks)	18	SMA-bilaterally 1Hz of 100% MT Sham-rTMS	Significant reduction in OCD symptoms in favor of rTMS compared to sham-rTMS.*
Sarkhel et al. 2010	RCT 10 sessions (5 days per week for 2 weeks)	42	PFC-R 10Hz of 110%MT Sham-rTMS	Significant reduction in OCD symptoms and a significant improvement in mood in both groups.* However, no significant difference was observed between groups.
PTSD				
Grisaru et al. 1998	Open study 1 session	10	Motor cortex-R of 0.3 Hz of 100% MT Motor cortex-L of 0.3 Hz of 100% MT	Significant reduction in anxiety and PTSD symptoms.*

Rosenberg et al. 2002	Open study 10 sessions (5 days per week for 2 weeks)	12	DLPFC-L 1Hz of 90%MT DLPFC-L 5 Hz of 90%MT	Significant improvement in insomnia, hostility and anxiety, but minimal improvements in PTSD symptoms.* However, no significant difference was noted between groups.
Cohen et al. 2004	RCT 10 sessions (5 days per week for 2 weeks)	24	DLPFC-R 1Hz of 80%MT DLPFC-R 10Hz of 80%MT Sham-rTMS	Significant improvement in PTSD symptoms and a significant reduction in general anxiety levels in favor of 10Hz-rTMS group when compared to other groups.*
Boggio et al. 2010	RCT 10 sessions (5 days per week for 2 weeks)	30	DLPFC-L 20Hz of 80%MT DLPFC-R 20Hz of 80%MT Sham-rTMS	Significant reduction in PTSD symptoms, anxiety and improvement in mood in favor of rTMS compared to sham-rTMS.*
PD				
Prasko et al. 2007	RCT 10 sessions (5 days per week for 2 weeks)	15	DLPFC-R 1Hz of 110%MT Sham-rTMS	Both groups showed a significant reduction in anxiety symptoms.* However, no significant difference was found between groups for PD symptoms.
GAD				
Bystrisky et al. 2008	Open study 6 sessions (2 days per week for 3 weeks)	10	DLPFC-R 1Hz of 90%MT	Significant reduction in anxiety symptoms.*
DEPRESSION				
Loo et al. 2009	RCT 4 sessions (2 days per week for 2 weeks)	38	PFC-L 10Hz of 110%MT Sham-rTMS	Significant reduction of mood symptoms in favor of 10Hz-rTMS when compared to sham-rTMS.*
Bortolomasi et al. 2007	RCT 5 consecutive sessions (1 week)	19	PFC-L 20Hz of 90%MT Sham-rTMS	Significant reduction of mood symptoms in favor of 20Hz-rTMS when compared to sham-rTMS.*
Rumi et al. 2005	RCT 20 sessions (5 days per week for 4 weeks)	46	DLPFC-L 5Hz of 120%MT Sham-rTMS	Significant augmented response to amitriptyline in favor of 5Hz-rTMS when compared to sham-rTMS.*
SCHIZOPHRENIA				
Mittrach et al. 2010	RCT 10 sessions (5 days per week for 2 weeks)	32	DLPFC-L 10Hz of 110%MT Sham-rTMS	Significant effects of 10Hz-rTMS to tolerability and safety and no deterioration of cognitive functions when compared to sham-rTMS.*
Bor et al. 2009	Case report 20 sessions (2 sessions per day during 5 days for 2 weeks)	1	DLPFC-L iTBS of 80%MT	iTBS seems to improve negative symptoms in schizophrenia.
Eberle et al. 2009	Case report 45 sessions (5 days per week for 9 weeks)	1	TPC-R cTBS of 80%MT TPC-L cTBS of 80%MT	cTBS seems to improve general psychopathology and global function.

*Significance level at ≤ 0.05

cTBS: continuous theta burst stimulation; DLPFC: dorso-lateral prefrontal cortex; L: left; GAD: generalized anxiety disorder; iTBS: intermittent theta burst stimulation; MT: motor threshold; OCD: obsessive compulsive disorder; PD: panic disorder; PFC: prefrontal cortex; PTSD: posttraumatic stress disorder; R: right; RCT: randomized clinical trial; rTMS: repetitive transcranial magnetic stimulation; SMA: supplementary motor area; TPC: temporoparietal cortex.

dyskinesia, whereas 5Hz-rTMS administered at 110% rMT for 15 min (900 pulses) induced a slight but non-significant increase. In a double-blind sham-controlled study, Hamada *et al.* [57] aimed to demonstrate that 5Hz-rTMS at 90% aMT over the SMA provide relief of motor symptoms in 98 PD patients. UPDRS results revealed that rTMS over SMA significantly improved bradykinesia in PD, supporting the hypothesis that neuronal activity of SMA is profoundly associated with hypokinetic symptoms in PD.

In a double-blind placebo-controlled study, Lomarev *et al.* [58] demonstrated that repeated sessions of 25Hz-rTMS administered at 100% rMT (1200 pulses/day) over the M1 and DLPFC bilaterally during four weeks (two sessions per week) improved motor functions (gait and bradykinesia) in PD patients that persisted for at least one month after the treatment ended. In line with this, Khedr *et al.* [59] demonstrated in early and advanced unmedicated PD patients that six consecutive sessions of 10Hz- and 25Hz-rTMS administered at 100% rMT (3000 pulses/day) applied to M1 bilaterally improve motor functions (UPDRS, walking time, key-tapping speed) in both early and advanced-PD groups, with a superiority in favor of 25Hz-rTMS compared to 10Hz-rTMS. Moreover, the effects lasted at least one month after the treatment. Another interesting study demonstrated that frequent sessions of 25Hz-rTMS applied at 100% rMT to M1 bilaterally augmented serum dopamine and improved motor functions (UPDRS) in 20 PD patients and that there was a correlation with sensorimotor functions [60].

Single-sessions of rTMS over the M1 have been argued to be a reliable treatment for improving sensorimotor functions in PD [61]. To determine which is the most effective rTMS protocol for PD sensorimotor functions rehabilitation, Filipovic *et al.* [62-63] conducted two sham-controlled, single-blinded, crossover studies. The first experiment, which included 10 PD patients, demonstrated that 1Hz-rTMS at 90% rMT delivered over the M1 for 4 consecutive days twice and sham-rTMS did not significantly differ; however, compared to the baseline, 1Hz-rTMS demonstrated a small but significant reduction in dyskinesia. The second experiment, using the same protocol, found no significant differences in sensorimotor symptoms, such as rigidity, bradykinesia and tremor.

Stroke

It is known that rTMS improves outcome after stroke by suppressing maladaptive cortical plasticity and improving adaptive cortical activity [64]. Neuroimaging studies show increased activity in undamaged brain areas in post-stroke patients [65]; however, the role of these areas remains controversial [66]. The activation of uninjured brain areas might reflect adaptive cortical reorganization, leading to functional recovery. On the other hand, some changes may be

maladaptive and generate the emergence of behaviors whose suppression would improve functional outcome. The symptoms after stroke are due to the changes in activity across the lesioned brain as to the actual lesion. For instance, contralesional neglect after stroke is not due to the lesion itself but directly to the hyperactivity of the intact hemisphere. Thus, the administration of 1Hz rTMS on the unaffected parietal lobe seems to be the best option to suppress the excitability of the intact hemisphere to promote balanced activity between hemispheres, improving contralesional visuospatial neglect after stroke [67].

Much of the spontaneous recovery from stroke after the acute phase involves neuroplastic changes. Neurorehabilitation aims to facilitate the neuroplasticity to speed up the improvement. Because the ideal recovery greatly depends on the neuroplasticity in the lesioned hemisphere, one therapeutic option is to increase neuroplasticity in the lesioned region through rTMS. In one study, 15 patients with chronic hemiparetic stroke performed a complex, sequential finger motor task using their paretic fingers after either 10Hz or sham-rTMS of the ipsilesional M1. Changes in the behavior and corticomotor excitability before and after the intervention were evaluated by measuring the movement accuracy, movement time and MEP amplitude. rTMS produced a significantly larger increase in MEP amplitude than the sham rTMS, and the plastic change was positively associated with enhanced motor performance accuracy. Another approach to brain stimulation is to target the contralesional side. The contralesional M1 inhibits the ipsilesional M1 via Transcallosal Inhibition (TCI) [68].

In a double-blind study, Liepert *et al.* [69] investigated whether inhibitory 1Hz rTMS over the contralesional M1 improved motor performance of the damaged hand in acute stroke. Twelve patients with a recent subcortical stroke (acute phase, 7 days) were submitted to a crossover design (1200 stimuli of real and sham rTMS). The protocol of stimulations was balanced across subjects and the stimulus intensity was subthreshold (90% motor threshold at rest). Motor function was tested by grip strength recordings and Nine Hole Peg Test (NHPT) performances before and after each rTMS session. When contrasted with sham stimulation, real rTMS enhanced NHPT results; however, no significant results for grip strength were observed in the damaged hand. No change in performance was recorded for the undamaged hand. NHPT baseline measures in a subgroup of patients suggested stable motor performance prior to the rTMS sessions. Such findings indicate that therapeutic rTMS applications over the contralesional hemisphere are viable in the acute phase of stroke and can transiently improve the dexterity of the damaged hand.

Another recent experiment examined the effect of inhibitory 1Hz rTMS applied over the M1 of the uninjured

hemisphere on the dexterity of the injured hand in subcortical stroke patients. All individuals performed a grasp, lift and hold task using an instrumented object and the index finger and thumb for both the injured and uninjured hand. This protocol was applied prior to baseline and following 1Hz rTMS over the vertex (control stimulation) and the M1 of the uninjured hemisphere. In contrast to baseline, 1Hz rTMS applied over the uninjured M1, excluding the vertex, enhanced the efficiency and timing of grasping and lifting with the injured hand. These findings suggest an interhemispheric competition concept and strengthen the argument in favor of rTMS as a novel tool for stroke rehabilitation [70].

Di Lazzaro et al. [71] recently evaluated the effects of TBS on cortical excitability in acute stroke, exploring the effects of facilitatory TBS of the damaged hemisphere and inhibitory TBS of the undamaged hemisphere on cortical excitability to single-pulse TMS bilaterally. To this end, the effects of TBS application in the patients were contrasted with those observed in the control group of age-matched healthy subjects. It was verified that both the facilitatory TBS in the damaged M1 and the inhibitory TBS in the undamaged M1 generated a significant increase in the amplitude of MEPs derived from stimulation of the damaged hemisphere. It was thus shown that facilitatory TBS over the stroke hemisphere and inhibitory TBS over the intact hemisphere, in the acute phase, augment the excitability of the damaged M1.

Depression

Depression is commonly accompanied by changes in cortical excitability mainly in prefrontal areas. These changes are responsible for dysfunctions spread in cortico-subcortical bihemispheric neural networks [72]. In this sense, it could be hypothesized that the stimulation of the PFC circuitries offer a therapeutic target [73]. Several investigations showed positive effects of rTMS over PFC on improvement in depressive symptoms. It is well known that rTMS applied over PFC for several weeks might have clear antidepressant effects; however, new studies are necessary to establish a consensus of its potential clinical utility [74].

The efficacy of rTMS use for reducing symptoms of treatment-resistant depression patients has been examined by several studies. Most of the studies demonstrated positive effects over PFC areas, in spite of their different methodologies [75-77]. For instance, the study of Loo et al. [77] assessed the efficacy and safety of 10Hz-rTMS administered at 110% MT over left PFC twice per week for 2 weeks. The study found a significant improvement in the symptoms when comparing patients who received rTMS to patients who received sham-rTMS. The results remained just after the end of the treatment (6 weeks of follow-up). Additionally, Bortolomasi et al. [76] demonstrated that 20Hz-rTMS at 90% MT over left

PFC applied on five consecutive days for 1 week results in antidepressant effects.

In addition, other studies aimed to verify the efficacy of rTMS treatment as an accelerating strategy, i.e., when combined with antidepressant drugs for treatment-resistant patients, and also observed positive effects of rTMS treatment over PFC in spite of their different methodologies [78-80]. For example, Rumi et al. [78] showed that the combination of 5Hz-rTMS at 120% MT over DLPFC with amitriptyline for 5 consecutive days for 4 weeks led to a significantly faster response. The study of Rossini et al. [79] investigated whether 15Hz-rTMS over left DLPFC for 2 weeks combined with antidepressants (i.e., venlafaxine, escitalopram or sertraline) for 5 weeks could augment the drug response. Positive results were found for rTMS combined with all antidepressants compared to the control group (i.e., drug and sham rTMS).

Schizophrenia

Schizophrenia is characterized by both negative and positive symptoms. The most common symptoms are auditory hallucinations. The experience of auditory hallucinations has been correlated on neuroimaging with increased activity in the primary auditory cortex of the middle and superior temporal gyri, along with speech areas in the left Temporo-Parietal Cortex (TPC) [81]. Based on the hypothesis that reduction of the neuronal activity in these regions may alleviate auditory hallucinations, some studies have applied low-frequency rTMS to left temporal-parietal and auditory cortex.

Low-frequency rTMS seems to be a potential option for inhibiting left TPC to alleviate auditory hallucinations. The meta-analysis of Aleman et al. [82] indicated that 1 Hz-rTMS is efficacious for resistant auditory hallucinations in schizophrenic patients, reducing auditory hallucinations, but has no effects on other positive symptoms or the cognitive deficits of schizophrenia. More recently, the systematic review of Poulet et al. [81] demonstrated that for the negative symptoms, most studies applied low-frequency rTMS to the left TPC when compared to sham-rTMS, inducing a substantial and significant reduction in hallucinations. However, this method did not have long-lasting effects, demanding a maintenance treatment. With regard to negative symptoms, the findings are inconsistent; however, some studies show improvement in negative symptoms regardless of the stimulation parameters used.

Another target area for treating negative symptoms in schizophrenic patients is the Prefrontal Cortex (PFC). For instance, in a sham-controlled study, Mittrach et al. [83] investigated the tolerability and safety of 10-Hz rTMS over the left Dorsolateral Prefrontal Cortex (DLPFC) with respect to cognitive functions and did not observe deterioration of cognitive functions. In addition, the comprehensive review of Fitzgerald

and Daskalakis [84] showed that there is no consensus about whether rTMS could play a role in reducing the negative symptoms of schizophrenia when applied over these areas.

TBS has also been therapeutically used in schizophrenia. Recent findings indicate that cTBS applied to the TPC reduces auditory verbal hallucinations [85, 86]. For instance, a case report showed that left cTBS reduced long-term persistent auditory hallucinations, which was accompanied by overall improvement in neuropsychological performance [85]. Similarly, a case report of paranoid schizophrenia demonstrated a complete remission of chronic, continuous, distressing voices following long-term bilateral application of cTBS to TPC. The patient had maintenance of rTMS effects at 3-month follow-up and a salient improvement in general psychopathology and global function [86].

Obsessive-Compulsive Disorders

Several neuroimaging studies had detected abnormalities involving mainly cortical and subcortical structures, such as the basal ganglia, Orbitofrontal Cortex (OFC), Supplementary Motor Area (SMA), DLPFC and, in particular, the caudate nucleus [87, 88]. Moreover, functional Magnetic Resonance Imaging (fMRI) studies suggested that OCD-related repetitive behaviors are caused by a reduction in cortical-subcortical inhibition and cortical hyperexcitability observed in regions of the PFC [89].

Within this context, a few reliable studies related to treatment of OCD symptoms were performed. Seven randomized controlled studies (i.e., using sham-coil) investigated the efficacy of rTMS on the reduction of OCD symptoms [28, 90-95]. However, few studies reported beneficial effects for OCD symptoms [92, 95].

With regard to the randomized controlled studies, Alonso et al. [90] administered 18 sessions (3 days per week for 6 weeks) of rTMS to 18 OCD patients (10 with rTMS and 8 with sham-rTMS) with 1 Hz-rTMS administered at 110% MT for 20 min (1200 pulses/day) over the right DLPFC. The authors found a slightly greater reduction in obsessions in the rTMS group; however, there was no significant difference between groups according to obsession or compulsion scales or the total scores of Y-BOCS and HAM-D. Similarly, Prasko *et al.* [93] administered 10 sessions (5 days per week for 2 weeks) of rTMS to 30 drug-resistant OCD patients (18 with rTMS and 12 with sham-rTMS) with 1 Hz-rTMS administered at 110% MT for 30 min (1800 pulses/day) over the left DLPFC. The result was a significant reduction in anxiety measures. Both the rTMS and sham-rTMS group displayed a significant reduction in measures on the HAM-A and Y-BOCS scales; however, no significant difference was found between the groups.

Sachdev et al. [94] administered 10 sessions (5 days per week for 2 weeks) of rTMS to 18 drug-resistant OCD patients

(10 with rTMS and 8 with sham-rTMS) with 10 Hz-rTMS administered at 110% MT for 15 min (1500 pulses/day) over the left DLPFC. After the 2 weeks, no significant reduction in anxiety symptoms was observed between the groups. Then, at the end of the treatment, patients were unblinded and given the option of an additional 2 weeks (10 sessions) of rTMS if they had received real-rTMS or 4 weeks (20 sessions) of rTMS if they had received sham-rTMS. After such further treatment, a significant reduction in obsessive symptoms was verified through the Y-BOCS scale.

Kang et al. [91] administered 10 sessions (5 days per week for 2 weeks) of rTMS to 20 drug-resistant OCD patients (10 with rTMS and 10 with sham-rTMS) with 1 Hz-rTMS administered at 110% MT for 20 min (1200 pulses/day) over the right DLPFC and sequentially at 100% MT for 20 min (1200 pulses/day) bilaterally over the SMA. There were no significant differences over 4 weeks between the rTMS and sham-rTMS groups on the YBOCS and the MADRS. These findings suggest that 10 sessions of sequential rTMS of the right DLPFC and the SMA at 1Hz-rTMS had no therapeutic effect on OCD symptoms.

Ruffini et al. [96] administered 15 sessions (5 days per week for 3 weeks) of rTMS to 23 drug-resistant OCD patients with 1 Hz-rTMS (16 with rTMS and 7 with sham-rTMS) administered at 80% MT for 10 min (600 pulses/day) over the left OFC [97]. There was a significant reduction in Y-BOCS scores when comparing rTMS to sham-rTMS for 10 weeks after the end of treatment; however, this effect was no longer apparent after 12 weeks. There was also a reduction in anxiety and depression symptoms, but not a significant difference between the two groups. The authors suggested that 1Hz-rTMS applied to the left OFC produced a significant but time-limited improvement in the OCD patients.

Mantovani et al. [92] administered 20 sessions (5 days per week for 4 weeks) of rTMS to 18 drug-resistant OCD patients (9 with rTMS and 9 with sham-rTMS) with 1 Hz-rTMS administered at 100% MT for 20 min (1200 pulses/day) bilaterally over the SMA [92]. At the end of the treatment, both non-responders to sham-rTMS and responders to active- or sham-rTMS received the option of an additional four weeks of open active-rTMS. After the additional 4 weeks, the response rate was 67% with the active- and 22% with the sham-rTMS. The patients who received 4 weeks of active-rTMS exhibited a 25% reduction in the Y-BOCS compared to a 12% reduction found in the sham-rTMS group. In those who received 8 weeks of active-rTMS, OCD symptoms improved by 50% on average. In addition, in the patients subjected to active-rTMS, the MT increased significantly in the right hemisphere over time. After 4 weeks of rTMS application, the abnormal hemispheric laterality found in the group randomized to active-rTMS was normalized.

Sarkhel et al. [95] administered 10 sessions (5 days per week for 2 weeks) of rTMS to 42 OCD patients with 10

Hz-rTMS (21 with rTMS and 21 with sham-rTMS) administered at 110% MT for 20 min over the right PFC [95]. They reported a significant reduction in OCD symptoms and a significant improvement in mood in both the rTMS and sham-rTMS group. However, the 10Hz-rTMS treatment was not superior to sham according to the Y-BOCS scores. The authors concluded that 10Hz-rTMS applied to right PFC did not have a significant effect in the treatment of OCD, but 10Hz-rTMS was modestly effective in the treatment of comorbid depressive symptoms in patients with OCD.

Post-Traumatic Stress Disorder

Neuroimaging studies have demonstrated that PTSD is associated with hyperactivity of the amygdala and hypoactivity in the PFC [97-101]. Several studies had indicated abnormalities involving the PFC, in particular the OFC and the DLPFC and limbic regions, particularly the right hemisphere [102-103]. Accordingly, rTMS applied to the PFC has been considered as a potential therapeutic technique for PTSD treatment [104]. Consequently, it was hypothesized that low-rTMS applied to the cortical areas of the right hemisphere would lead to decreased activity in those areas, which could contribute to the treatment of the functional cerebral abnormalities associated with PTSD [105, 42]. Accordingly, two controlled studies were conducted [102, 106].

Cohen et al. [102] administered 10 sessions (5 days per week for 2 weeks) of rTMS to 24 PTSD patients with 1Hz-rTMS (n=8), 10Hz-rTMS (n=10) or sham-rTMS (n=6) administered at 80% MT for 20 min over the right DLPFC [102]. The group that was treated with 1Hz-rTMS received 100 stimuli per day, in contrast to 10Hz-rTMS and a sham-rTMS group, which received 400 stimuli per day. When compared to the other groups, the 10Hz-rTMS group showed improvements in PTSD symptoms (re-experiencing and avoidance) on the PTSD Checklist and Treatment Outcome for PTSD scale. Furthermore, a significant reduction of anxiety levels, lasting for 14 days, was observed.

Boggio et al. [106] administered 10 sessions (5 days per week for 2 weeks) of rTMS to 30 PTSD patients (20 with rTMS and 10 with sham-rTMS) with 20 Hz-rTMS administered at 80% MT for 20 min (1600 pulses/day) over the left (n=10) and right PFC (n=10). The authors showed that 20Hz-rTMS applied to both left and right DLPFC compared to sham-rTMS led to a significant decrease in PTSD symptoms according to the PTSD Checklist and Treatment Outcome PTSD Scale. However, 20Hz-rTMS applied to the right DLPFC had a larger effect compared to that applied to the left DLPFC, remaining long lasting and significant at the 3-month follow-up. Moreover, a significant improvement in mood after application of 20Hz-rTMS to the left DLPFC and a significant reduction in anxiety following application to the right DLPFC were reported.

Panic Disorder

Neuroimaging studies have verified that the DLPFC and amygdala are involved in PD [107-110]. After an extensive search for reliable evidence, only one controlled study was found. Prasko et al. [111] administered 10 sessions (5 days per week for 2 weeks) of rTMS to 15 drug-resistant PD patients (7 with Hz-rTMS and 8 with sham-rTMS) with 1 Hz-rTMS administered at 110% MT for 30 min (1800 pulses/day) over the right DLPFC. All participants exhibited a reduction in anxiety symptoms, as verified by the CGI, Panic Disorder Severity Scale (PDSS), HAM-A and Beck Anxiety Inventory (BAI); however, no significant differences in PD symptoms were found between the treatment and sham groups.

In conclusion, the rTMS technique is a non-invasive and effective methodology with potential for therapeutic use. In this review, we have cited several studies of patients with Parkinson's disease, stroke, generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder, depression and schizophrenia that have showed that rTMS can improve some symptoms associated with these conditions. rTMS might be useful for promoting cortical plasticity in patients with these conditions. However, these changes are transient and it is premature to propose these applications as realistic therapeutic options, even though the rTMS technique has been evidenced as a potential modulator of neuroplasticity. Although positive results have frequently been reported in randomized controlled studies, several treatment parameters, such as location, frequency, intensity and duration, have been used unsystematically. Thus, the interpretation of the results is difficult and little guidance is provided concerning what treatment parameters (i.e., stimulus location and frequency) may be the most useful for treating these disorders. In addition, functional imaging of the region of interest could highlight the capacity of rTMS to bring about plastic changes of the cortical circuitry and hint at future novel clinical interventions. Thus, we recommend that further studies clearly determine the role of rTMS in the treatment of these conditions. Finally, we must remember that however exciting the neurobiological mechanisms might be, the clinical usefulness of rTMS will be determined by its ability to provide patients with neurological and psychiatric disorders with safe, long-lasting and substantial improvements in quality of life.

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