The Value of Repetitive Transcranial Magnetic Stimulation (rTMS) for the Treatment of Anxiety Disorders: An Integrative Review

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Abstract: Unlike for depression, only few studies are available today investigating the therapeutic effects of repetitive transcranial magnetic stimulation (rTMS) for anxiety disorders. This review aims to provide information on the current research approaches and main findings regarding the therapeutic use of rTMS in the context of various anxiety disorders. Although positive results have frequently been reported in both open and randomized controlled studies, our review of all identified studies indicates that at present no conclusive evidence of the efficacy of rTMS for the treatment for anxiety disorders is provided. Several treatment parameters have been used, making the interpretation of the results difficult. Moreover, sham-controlled research has often been unable to distinguish between response to rTMS and sham treatment. However, there is a limitation in the rTMS methods that likely impacts only the superficial cortical layers. It is not possible to directly stimulate more distant cortical areas, and also subcortical areas, relevant to the pathogenesis of anxiety disorders, though such effects in subcortical areas are thought to be indirect, *via* trans-synaptic connections. We thus recommend further studies to clearly determine the role of rTMS in the treatment of anxiety disorders. Key advances in combining TMS with neuroimaging technology may aid in such future developments.

Keywords: Anxiety, generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder, repetitive transcranial magnetic stimulation, rTMS, social anxiety disorder.

INTRODUCTION

One of the most frequent groups of psychiatric disorders is the group of anxiety disorders [1], with lifetime prevalence greater than 20% [2]. Anxiety disorders subsume obsessive-compulsive disorder (OCD), panic disorder (PD), post-traumatic stress disorder (PTSD), generalized anxiety disorder (GAD) and social anxiety disorder. These disorders can be very debilitating and although the available methods of treatment are safe and effective (i.e., pharmacotherapy, psychotherapy and cognitive-behavioral therapy), high rates of non-responders to treatment are reported (approximately 25% of patients) [3]. With advances in the understanding the neurobiological mechanisms involved in anxiety disorders, new treatments have been espoused. One such treatment method is transcranial magnetic stimulation (TMS), originally introduced in 1985 as a method for non-invasive focal brain stimulation [4]. 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 [5]. Within this context, TMS in its repetitive form, i.e. 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 [6, 7].

The application of rTMS generates clear effects on a range of measures of brain function and has become an important research tool in neuropsychiatry treatment [8-10]. With this in mind, the treatment with rTMS can be considered a brain-system-based neuromodulation treatment due to its focus on directly targeting the

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1871-5273/11 $58.00+.00

neural circuitry of the disorders. rTMS shifts the perspective of treatment from changing the neurochemistry within the synapse, to altering or modulating the function of the neural circuitry in the brain that is believed to be disorganized in certain disorders [11, 12]. Even though there is now a growing interest in the research of new treatment for anxiety disorders, the main focus of the possible therapeutic effects of TMS is mainly in the domain of depression [13, 14].

Based on the idea of an interhemispheric imbalance and/or deficit in the limbic-cortico control as a model for human anxiety [3], the use of 1Hz-rTMS on the prefrontal cortex (PFC) has demonstrated effects in some studies involving healthy individuals, patients with PTSD and PD [15]. However, Pallanti and Bernardi [16] also argued that rTMS over the right dorsolateral prefrontal cortex (DLPFC), especially above 5Hz-rTMS, reduces the symptoms of anxiety in PTSD and PD. Therefore, to further elucidate the putative anxiolytic action of rTMS in anxiety patients future studies have to be conducted.

This review paper aims to provide information on the current research and main findings related to the potential therapeutic effects of rTMS in anxiety disorders. We will review the physical and neurophysiological concepts of TMS, the main findings of rTMS from animal models, the importance of the effects of sham-rTMS and stimulation parameters, and the experimental advances of rTMS that can become viable as clinical applications in the coming years related to the treatment of anxiety disorders. With this in mind, we developed a strategy for searching studies in the main data bases. The computer-supported search used the following databases: *Scielo, Pubmed/Medline, ISI Web of Knowledge, PsycInfo* and *Cochrane Library*. The search terms *Panic disorder, Obsessive-Compulsive disorder, Post-traumatic stress disorder, Generalized anxiety disorder, Social anxiety disorder* were used in combination with *transcranial magnetic stimulation, TMS, repetitive transcranial magnetic stimulation, rTMS, motor threshold, motor evoked potential, MEP, cortical excitability, neuroimaging*. In addition, all reports including reviews, meta-analyses and controlled randomized clinical trials and open label trials, book chapters are also cited to provide readers with more details and references than can be accommodated within this paper. Discussion has been focused mainly on studies published in English and reported in the past 12 years but also included commonly referenced studies relevant to the neurobiology of the diseases and possible rationales for rTMS application.

PHYSICAL AND PHYSIOLOGICAL CONCEPTS OF TMS

There are several key concepts in the field of TMS that are closely related to its clinical efficacy [17]. TMS was introduced by Anthony Barker in 1985 as a non-invasive, safe and painless method, in order to activate human motor cortex and to assess the human central motor pathways [4]. The main concept of TMS relies on Faraday's law of electromagnetic induction, where an electrical current is applied over the scalp through a magnetic coil. 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 [18]. The TMS coil is usually round or figure-eight (butterfly) in shape, with which the latter produces a stronger and more focal field than the circular coil. Continuing 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, lasting 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 [17, 19-21].

The precise effect of the stimulation on neuronal activity remains unclear; however, it is assumed that the large magnetic stimulus (duration of ~ 100μs) synchronously excites a population of neurons, provoking a rapid change in firing of impulses for a few milliseconds after which the entire activity is suppressed by a long-lasting period of GABAergic inhibition [22]. 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 [23]; however, another parameter influencing rTMS effects is probably the stimulation frequency.

There are two common types of rTMS stimulation; high frequency rTMS (> 5 Hz) and low frequency rTMS (< 1 Hz). High frequency rTMS has been evidenced to wield facilitating effects on neuronal excitability. Unlike high frequency rTMS, low frequency rTMS (< 1 Hz) has inhibitory effects on neuronal excitability [5, 24]. These inhibitory and excitatory effects have been proposed to be related to long term potentiation and long-term depression (LTD) [19, 25, 26]. For instance, the study performed by Chen *et al*. [27], showed that rTMS administered at 0.1 Hz for 1 hour in healthy humans did not change cortical excitability. However, rTMS administered at 0.9 Hz for 15 minutes (810 pulses), similar to the parameters used to induce LTD in animal studies, led to a significant decrease in motor evoked potential (MEP) amplitude of 19.5%, lasting for at least 15 minutes after the end of the stimulation. This finding may be considered similar to LTD. Even though the parameters of stimulation can be consistent across individuals, for a given individual, differences related to stimulation can be observed [24]. The most common way to verify the intensity of the stimulation has usually been to calibrate across individuals by testing the minimal intensity of stimulation applied to the primary motor cortex (i.e., M1 area) that evokes a motor response (i.e., MEP) [17]. These MEPs can be used to define the motor threshold (MT), defined as the lowest stimulation intensity over the M1 area needed to induce an MEP in an extremity muscle in at least 5 out of 10 consecutive trials [28].

The MT is well-documented as an objective and standardized measure of human corticospinal excitability that is, widely used to standardize intensities of stimulation and, commonly defined in terms of a percentage of the device's available output or in Tesla (T) [29]. Most of the studies have used a standard procedure of positioning the coil over the head and identifying the motor cortical site (i.e., hot spot, defined as the location of the calculated strongest electric-field) for optimal stimulation of the abductor pollicis brevis muscle by measuring 5 cm anterior along the skull surface in a parasagittal line (i.e., posterior-anterior direction) [9, 17]. 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 [30]. Moreover, there are other rTMS parameters that must be to take 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 [31, 32].

ANXIETY DISORDERS AND rTMS: FINDINGS FROM ANIMAL MODELS

rTMS holds the potential to selectively modulate brain circuitries involved in pathological processes such as post-traumatic stress disorder, obsessive-compulsive disorder, panic disorder, generalized anxiety disorder and social anxiety disorder [15, 16]. Preliminary studies using rTMS have provided largely inconclusive evidence of symptom relief in obsessive–compulsive disorder [33, 34] and panic disorder [35]. Moreover, rTMS has great potential as an additional option combined with psychotherapy and/or drugs to psychotherapy and drug treatments, especially since TMS has only very little treatment discomfort and no lasting side effects,

comparing it favorably with many somatic treatments [15]. However, using TMS in clinical practice is essential in order to know how it acts on brain tissue in terms of, the putative neurobiological changes underlying the observed clinical effects [16, 36, 37]. Within this context, the limitations of human research require appropriate pre-clinical studies in animal models. In addition, basic studies are needed at the cellular and molecular level in order to better understand the regulation of the induced intracerebral current density, unraveling which elements involved in this regulation may serve as potential treatment targets [38].

In animal studies rTMS has been reported to provide benefit in some anxiety-related disorders [39, 40]. An experiment by Kanno *et al*. [40] demonstrated that the intensity of stimulation is a critical factor in the anxiolytic-like effects as assessed by the elevated plus-maze (EPM) test in male Wistar rats. Chronic rTMS treatment (3 days) provided better anxioltyic-like effects in the EPM than in rats exposed to acute rTMS treatment. In addition, repeated rTMS suppressed the increase in extracellular serotonin (5-HT) levels induced by the EPM test, but did not influence the elicited dopamine (DA) levels. These data suggest that chronic treatment with rTMS over the frontal areas has anxiolytic-like effects in rats, which are related to the serotonergic neuronal system. Other EPM studies were less successful. For example, Keck *et al*. [39, 41] reported that chronic rTMS treatment had no effects in male Wistar rats and was anxiogenic in rats selectively bred for low anxiety-related behaviors, using the EPM test, although the treatment did appear to have antidepressant-like effects showing an attenuated stress-induced elevation of plasma corticotrophin (ACTH) concentrations in the forced-swim test. However, Hedges *et al*. [42, 43] contradicted the findings of Keck *et al*. [39], showing no differences on the performance of the same task between animals treated by TMS and sham-TMS.

In general, results from animal models of anxiety-related disorders have demonstrated an antidepressant effect of rTMS with some consistency. For instance, in studies using the forced swim test (the most widely used preclinical antidepressant test), rTMS demonstrated a robust treatment-induced antidepressant effect in anxious rodents [39, 42, 44, 45]. For this reason, it has been suggested that the observed benefit of TMS in some studies may be due to relief of depressive symptoms rather than being specific to the anxiety itself [43].

Most of the rodent studies performed have been limited in their applicability to the physical rTMS specifications used for humans. That is, due to certain factors, such as the coil size, rTMS cannot be focally delivered in rodents, and in that case the entire brain receives the stimulation. Because of this and other limitations, e.g., handling procedure, sound of magnetic stimulator, and direct effects of rTMS on the muscles, rTMS application is considered to be more focal in humans than in rodents [46]. Moreover, sham-controlled conditions are required in the studies in order to provide a safe interpretation regarding effects of rTMS on anxiety symptoms. Thus, it has been suggested that the efficacy, validity and usefulness of rTMS in studies with rodents so far is questionable because few studies used sham-controlled conditions and because of other limitations already cited above [47].

EFFECTS OF SHAM-rTMS AND STIMULATION PARAMETERS

An 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 [48]. Within this context, different control conditions can be used to try and ensure that changes in performance be ascribed to rTMS effects upon a specific brain area. One of the most common strategies is the use of sham stimulation (sham-rTMS) [49]. rTMS is indeed associated with a number of sensory perceptions that can nonspecifically interfere with task performance. For instance, the discharging coil produces a click sound that may induce arousal, thereby modulating task performance, irrespective of the experimental demands (i.e., *via* intersensory facilitation) [50]. An alternative way that is routinely used in the cognitive TMS literature is vertex stimulation because the auditory and somatosensory activations caused by vertex TMS can be equivalent to those of real TMS. Of course, the underlying assumption is that vertex TMS does not affect the cognitive network active during task execution [51, 52].

In general, sham-rTMS has been applied by tilting the coil away from the scalp [53], so that both sound and scalp contact are roughly similar to those experienced during active stimulation, whereas the magnetic field does not reach cortical neurons or cutaneous receptors or superficial muscles. Although sham coils produce an analogous sound artifact, they do not induce the same scalp sensations or muscle twitches, so that they can rest tangential to the scalp surface, exactly as they are during active stimulation [54, 55]. Another important consideration that must be taking into account in order to determine the specific efficacy of rTMS in clinical trials and to create a credible placebo (i.e., sham-rTMS) condition, is that patients in randomized trials should be naive to rTMS, in other words, rTMS studies should not have a crossover design. With respect to this issue, the ideal sham condition should not have a real stimulation effect, and it should not be recognized as sham by patients, particularly when considering that real stimulation conditions come along with rTMS specific side effects. In line with that, Herwig *et al*. [56] investigating the antidepressant effects of rTMS, asked for patients to give their impression whether they received the sham or the real treatment, and if they would recommend the treatment to others. From 15 patients with real stimulation, 11 suggested that they obtained true stimulation, and 4 to have obtained sham. From 14 sham stimulated subjects, 9 suggested that they obtained the real condition and 5 to have been sham stimulated. There was no significant difference between these and in addition, the majority of patients in both stimulation conditions would recommend rTMS to others. In both conditions, the majority of subjects believed they had received the real condition. This implies suitability of the sham condition used since subjects appeared not to be able to accurately identify or differentiate this condition from sham. The results imply the feasibility of a valid sham condition with a "real" coil.

However, there is evidence that some types of sham manipulations used in clinical trials actually do exert some effects on the brain [57, 58]. The tilting does reduce any discomfort from scalp stimulation associated with active rTMS and, thus, may have the potential to interfere to some degree with the adequacy of study blinding. Studies guard against this by recruiting only rTMS-naive patients, so that subjects are not cued to discriminate between active and sham conditions based on scalp sensation. Even if a form of coil-tilt sham that does not exert measurable brain effects is used, studies rarely report data on the integrity of the blind on the part of the patients and raters. It is reasonable to assume that crossover trials with coil-tilt sham conditions are likely to be unblinded because active and sham rTMS do not feel the same [59, 60]. Other option include the one used in a recent experiment consisting of a sensor strip between the electromagnet and the scalp, which can counter-stimulate during pulse delivery so as to reduce the scalp sensation perceived from active rTMS [61].

The matter of placebo effects is especially important in some conditions, such as studies investigating the efficacy of treatments [49]. For such purposes alternative methods of brain stimulation to provide suitable control conditions have been proposed. For instance, Rossi *et al*. [62] developed a new method of sham stimulation, known as real electromagnetic placebo, in which a fake coil (made of wood) with the same shape as a real coil is attached to the real coil. This fake coil has two functions: to block the magnetic field from the real coil, and to house a bipolar electrical stimulator in contact with the scalp. This device is more likely to be judged as

real stimulation by naive TMS subjects. The difficulty in blinding TMS makes the comparison of TMS with a gold standard treatment (e.g., psychopharmacology) complex. In the case of pharmacologic agents, it would be possible to use a "double-dummy" design in which some patients would receive sham rTMS plus active medication, whereas other patients would receive active rTMS and a placebo pill. An additional challenge in the design of clinical trials with rTMS pertains to the standardization of the dosage. Just as it is critical to control the dosage of medication administered during drug trials, it is likewise essential to control the amount of rTMS administered and the location of the brain region stimulated [63].

Other important considerations to be taken into account are the parameters of stimulation, e.g., pulse width, number of stimulation sessions, frequency, intensity and site of stimulation [31]. A protocol composed of repeated sessions may be superior to a single session, due to its cumulative effect related to amount of stimulation required to induce a sustained effect. Indeed, although some studies have shown a relatively long-lasting effect (i.e., of 2 weeks), this period is short if the goal is to induce a clinically meaningful result. Maintenance treatments or other patterns of stimulation that might induce longer-lasting modulation of cortical excitability should be explored. One possibility is to increase the total number of sessions, as in a recent study of major depression, in which up to 30 sessions of rTMS were administered [64]. Novel patterns of stimulation, for example primed 1 Hz stimulation [65] or theta burst stimulation [66], might offer advantages, as they seem to induce longer-lasting long-term-depression-like phenomena. Careful consideration of cortical targets seems to be critical, and this might need to be individualized for each patient and underlying pathology.

In summary, a number of parameters need to be taken into account in order to optimize the clinical effects of rTMS. 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, seems to be a crucial procedure to adopt [48, 49].

EFFECTS OF rTMS ON ANXIETY DISORDERS

Anxiety is a normal adaptive response to stress that allows coping with adverse situations. However, when anxiety becomes excessive or disproportional in relation to the situation that evokes it or when there is not any special objects directed at it, such as an irrational dread of routine stimuli, it becomes a disabling disorder and is considered to be pathological [67, 68]. The term "anxiety disorders" subsumes a wide variety of conditions of abnormal and pathological fear and anxiety, including OCD, PTSD, PD and GAD [15, 16]. The anxiety disorders comprise the most frequent psychiatric disorders and can range from relatively begnign feelings of nervousness to extreme expressions of terror and fear.

The first evidence of a putative anxiolytic action of rTMS in humans came from studies with health subjects [69, 70] based on the theory so called ''valence-hypothesis'', which has been formerly proposed for human anxiety [71]. According to this model, withdrawal-related emotions such as anxiety are located in the right hemisphere, whereas approach related emotions such as joy or happiness are biased to the left hemisphere. Along with this hypothesis, there is some evidence that anxiety disorders might be associated with increased right-hemispheric activity [71]. With this in mind, Schutter *et al*. [69] and van Honk *et al*. [70] then conducted placebo-controlled experiments in healthy subjects using rTMS. Schutter *et al*. [69], showed that 1Hz-rTMS at 130% MT in the right DLPFC, compared to sham-rTMS, resulted in a decrease in self-rated anxiety along with a contralateral increase in theta-EEG activity. Similarly, van Honk *et al*. [70] demonstrated that 1Hz-rTMS at 130% MT in the right DLPFC reduced the vigilant emotional response to fearful faces, but only in the unmasked fearful faces. Taken together, these findings suggest that a decrease in right frontal activity might normalize the interhemispheric imbalance present in anxiety disorders.

Other studies set out to investigate the hypothesis of high-rTMS efficacy in anxiety disorders treatment. Specifically, the cerebral hyperexcitability and behavioral or cognitive activation observed in neuropsychiatric disorders support this hypothesis [72]. The rationale for using high-rTMS is based on the study of George *et al*. [73]. The authors demonstrated that the activity of fronto-subcortical circuits can arguably be diminished by increasing the activity in the indirect pathway by stimulating the left DLPFC by high-rTMS. In this section, we will discuss the anxiety disorders, including PD, GAD, OCD, PTSD. We will give a brief description and present the main findings of rTMS treatment for each disorder (see Table **1**).

OCD

The main symptoms of OCD are obsessions (e.g., ideas, thoughts, impulses or persistent images) that are experienced by the patients as intrusive are associated with compulsions (e.g., repetitive behaviors, like washing the hands; or mental acts, like prayer). On the whole, individuals with obsessions, attempt to suppress or neutralize them with other behavior, such as thoughts or actions [68].

With regard to the brain circuits involved in OCD, several 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 [74, 75]. Moreover, functional magnetic ressonance 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 prefrontal cortex [76].

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 [77-83]. However, only 5 studies reported beneficial effects for OCD symptoms [82, 83]. In addition to these studies, another 3 non-controlled studies investigating effects of rTMS on OCD symptoms, reported significant findings [33, 84, 85].

With respect to non-controlled studies, in an intra-individual crossover study, Greenberg *et al*. [84] administered 1 session of rTMS to 12 OCD patients, with 20 Hz-rTMS administered at 80% MT for 20 min (800 pulses) over the left and right PFC and the occipital cortex on separate days. Both obsession and compulsion were assessed before, during, 30 minutes after and 8 hours after each application using the Yale Brown Obsessive Compulsive Scale (Y-BOCS), Hamilton Rating Scale for Depression (HAM-D), and Hamilton Rating Scale for Anxiety (HAM-A). Compulsive symptoms improved until 8 hours after rTMS application over the right PFC. However, application of rTMS to the left PFC resulted in a shorter-lasting (i.e., 30 minutes) and non-significant reduction in compulsive symptoms. Moreover, mood improved during and 30 minutes after rTMS application over the right PFC. Compulsive symptoms also improved after rTMS applied to the OCC, although not significantly.

In open study, Sachdev *et al*. [33] administered 10 sessions (5 days per week 2 weeks) of rTMS to 12 drug-resistant OCD patients, with 10 Hz-rTMS administered at 110% MT for 15 min (1500 pulses/day) over the left (n = 6) or right PFC (n = 6). Patients were assessed at baseline and after 1 and 2 weeks of stimulation, and 1

Table 1. Summary of Open and Controlled Studies of rTMS as a Treatment of Anxiety Disorders, Including OCD, PTSD, PD and GAD

Study	Design	N	rTMS Protocol	Efficacy
OCD				
[84]	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.*
[33]	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.
[77]	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.
[85]	Open study 10 sessions (5 days per week for 2 weeks)	10	SMA–bilaterally 1Hz of 100% MT	Significant reduction in OCD symptoms.*
[78]	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.
[79]	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 having received rTMS showed a significant reduction in OCD symptoms.
[80]	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 on both groups or between groups.
[81]	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.
[82]	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.*
[83]	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				
[100]	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.*
[101]	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 of insomnia, hostility and anxiety, but minimal improvements in PTSD symptoms.* However, no significant different was noted between groups.
[86]	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 of PTSD symptoms and a significant reduction in general anxiety levels in favor of 10Hz-rTMS group when compared to other groups.*
[88]	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 of mood in favor of rTMS compared to sham-rTMS.*
PD				
[87]	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				
[109]	Open study 6 sessions (2 days per week for 3 weeks)	10	DLPFC–R 1Hz of 90% MT	Significant reduction in anxiety symptoms.*

*Significant level at ≤ 0.05

DLPFC: dorso lateral prefrontal cortex; L: left; GAD: generalized anxiety disorder; MT: motor threshold; OCD: obsessive compulsive disorder; PD: panic disorder; PTSD: posttraumatic stress disorder; R: right; RCT: randomized clinical trial; rTMS: repetitive transcranial magnetic stimulation; SMA: supplementary motor area.

month after the completion of the treatment by Y-BOCS, Montgomery-Asberg Depression Rating Scale, Beck Depression Inventory and the Spielberger State Anxiety Rating. Both groups showed significant reductions in obsessions and compulsions as rated on the Y-BOCS scale after 2 weeks of rTMS application, however, no significant differences were found between the groups. The improvement in the obsessions persisted until one month after rTMS treatment according to the results of Y-BOCS subscales.

More recently, Mantovani and colleagues [85] administered 10 sessions (5 days per week for 2 weeks) of rTMS to 10 patients (5 with OCD and 5 with Tourette's syndrome), with 1 Hz-rTMS administered at 100% MT for 26 min (1200 pulses/day) bilaterally over the supplementary motor area. Suggestions of clinical improvement were apparent as early as after the first week of rTMS. After the second week of treatment, statistically significant reductions were still detected with the Y-BOCS, Yale Global Tic Severity Scale, Clinical Global Impression-Severity of Illness (CGI-S), HAM-D, HAM-A, Beck Depression Inventory, Scale for Autoevaluation of Depression, Impact of Events Scale and Symptoms Checklist and Social-Adaptation Self-evaluation Scale. Symptom improvement was correlated with a significant increase of the right resting motor threshold and was stable at 3 months follow-up. 1Hz-rTMS applied to the SMA resulted in significant clinical improvement and normalization of the right hemisphere hyperexcitability, thus, re-establishing hemispheric symmetry in MT.

With regard to the randomized controlled studies, Alonso *et al*. [77] administered 18 sessions (3 days per week for 6 weeks) of rTMS to 18 OCD patients (10 for rTMS and 8 for sham-rTMS), with 1 Hz-rTMS administered at 110% MT for 20 min (1200 pulses/day) over the right DLPFC. Assessments were performed at baseline and weekly until 10 weeks after rTMS. A slightly greater reduction in obsessions was found in the rTMS group; however there was no significant difference between groups according to obsession or compulsion scales and total scores of Y-BOCS and HAM-D.

Similarly, Prasko *et al*. [78] administered 10 sessions (5 days per week for 2 weeks) of rTMS to 30 drug-resistant OCD patients (18 for rTMS and 12 for sham-rTMS), with 1 Hz-rTMS administered at 110% MT for 30 min (1800 pulses/day) over the left DLPFC. Patients were rated before the treatment (week 0), after 10 days of stimulation (week 2) and 2 weeks after stimulation (week 4) on CGI, HAM-A, BAI, Y-BOCS. Rating scales were administered the day before the first rTMS administration, then after 2 weeks (after 10 stimulation) and again after 4 weeks (2 weeks after last stimulation). The result was a significant reduction in anxiety measures. Both rTMS- and sham-rTMS groups 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*. [79] administered 10 sessions (5 days per week for 2 weeks) of rTMS to 18 drug-resistant OCD patients (10 for rTMS and 8 for 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 groups. Then, at the end of the treatment, patients were unblinded and given the option of a further 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*. [80] administered 10 sessions (5 days per week for 2 weeks) of rTMS to 20 drug-resistant OCD patients (10 for rTMS and 10 for 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 supplementary motor area. There were no significant differences over 4 weeks between the rTMS and sham-rTMS groups on the YBOCS and the Montgomery-Asberg Depression Rating Scale. 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.

Ruffini *et al*. [81] administered 15 sessions (5 days per week for 3 weeks) of rTMS to 23 drug-resistant OCD patients, with 1 Hz-rTMS (16 for rTMS and 7 for sham-rTMS) administered at 80% MT for 10 min (600 pulses/day) over the left OFC. The OCD symptoms, mood, and anxiety were rated at baseline, at the end of treatment, and once every 2 weeks at the 3-month follow-up. There was a significant reduction in Y-BOCS scores when comparing rTMS to sham-rTMS for 10 weeks after the end of treatment: 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 2 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*. [82] administered 20 sessions (5 days per week for 4 weeks) of rTMS to 18 drug-resistant OCD patients (9 for rTMS and 9 for sham-rTMS), with 1 Hz-rTMS administered at 100% MT for 20 min (1200 pulses/day) bilaterally over the SMA. At the end of the treatment, both, non-responders to sham-rTMS and responders to active- or sham-rTMS received the option of a further 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 sham-rTMS group. In those who received 8-weeks of active-rTMS, OCD symptoms improved on the average by 50%. In addition, in the patients subjected to active-rTMS, the MT increased significantly over time in the right hemisphere. After 4 weeks of rTMS application, the abnormal hemispheric laterality found in the group randomized to active-rTMS was normalized.

Sarkhel *et al*. [83] administered 10 sessions (5 days per week for 2 weeks) of rTMS to 42 OCD patients, with 10 Hz-rTMS (21 for rTMS and 21 for sham-rTMS) administered at 110% MT for 20 min over the right PFC. The results were rated on YBOCS, HAM-D, HAM-A and CGI-S at baseline, day 14 and day 28. They reported a significant reduction in OCD symptoms and a significant improvement in mood in both rTMS and sham-rTMS groups. 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 significant effect in the treatment of OCD, but, that, 10Hz-rTMS was modestly effective in the treatment of comorbid depressive symptoms in the patients with OCD.

In conclusion, the significant number of drug-resistant patients suffering from OCD makes a continuation of research on alternative treatment approaches necessary and important. Yet, until today the findings reported above do not support that rTMS, as hitherto applied, is an effective treatment for OCD, since only 2 sham-controlled studies yielded positive results [81, 82]. Regarding the treatment courses, these appear to be inadequate. In the literature on the therapeutic rTMS effects in depression, it is clearly suggested that 4 weeks (i.e., 20 sessions) of rTMS administered on consecutive weekdays are necessary for achieving consistent antidepressant effects. In contrast, in the OCD studies, only Alonso *et al*. [77] and Mantovani *et al*. [82] assessed the effects of rTMS compared to sham-rTMS over at least 4 weeks. However, rTMS was only given three-times per week by Alonso *et al*. [77], in contrast to Mantovani *et al*. [82] that administered rTMS five-times per week.

At least 2 studies may have been underpowered, suggesting that results may be attributed to a type II error [77, 78]. The low placebo response reported in OCD patients supports this suspicion. However, Sachdev *et al*. [79] noted that given the effect size in

their study, a very large sample would have been required to demonstrate a group difference. In addition, all sham-controlled studies used methods that are recognized to provide adequate blinding (active coil, 45° or 90° to the head or inactive coil on the head with active coil discharged in 1 m-distance) [77-83, 86-88].

Six of these studies controlled for antidepressant effects [78, 79, 81-83, 88]. This is important, since application of rTMS to the PFC has antidepressant effects [60, 89] and since comorbid depression is common in patients with OCD [90]. As such, it is very difficult to assess the effects of rTMS on OCD independent of depression.

The neural circuitry underlying OCD is not exclusively cortical. Thus, given that rTMS is a focal treatment that is known to result in cortical depolarization up to a depth of 2 cm, it is unlikely that the application of rTMS to the PFC is sufficient to modify abnormal subcortical circuitry in OCD, despite known trans-synaptic effects [91].

Nonetheless, the current findings provide sufficient grounds to justify further investigations into the potential therapeutic applications of rTMS for OCD. These future studies should be well controlled using a more sophisticated sham system in larger samples in order to confirm or falsify the therapeutic effect of rTMS in obsessive-compulsive disorder.

PTSD

The main symptoms of PTSD include intrusive memories, flashbacks, hypervigilance, sleep disturbance, avoidance of traumatic stimuli, physiological hyperresponsivity and numbing of emotions and social dysfunction [16]. Neuroimaging studies have demonstrated that PTSD is associated with hyperactivity of the amygdala and hypoactivity in the PFC [92-96]. Several studies had indicated abnormalities involving the PFC, in particular the OFC and the DLPFC, and limbic regions, particularly the right hemisphere [86, 97, 98]. Accordingly, rTMS applied to the PFC has been considered as a potential therapeutic technique for PTSD treatment [99]. Cosequently, it was hypothesized that low-rTMS applied to the cortical areas of the right hemisphere would lead to a decreased activity in those areas, which could contribute to the treatment of the functional cerebral abnormalities associated with PTSD [15, 16]. Accordingly, 2 non-controlled studies [100,101] and 2 controlled were conducted [86, 88].

Grisaru *et al*. [100] administered 1 session of rTMS to 10 PSTD patients, with 0.3 Hz-rTMS administered at 100% MT for 35 min (450 pulses) to left and right M1 on the same day. The patients were assessed at four time points: 2 hours before, rTMS (baseline), 24 hours following rTMS, and 1 week and 28 days after the single session. rTMS application led to a significant reduction in PTSD symptoms (i.e., avoidance, anxiety and somatization) as reflected in both the Symptoms Checklist and CGI-S. These effects lasted for 24 hours to 28 days.

Rosenberg *et al*. [101], administered 10 sessions (5 days per week for 2 weeks) of rTMS to 12 drug-resistant patients with PSTD and depression, with 1 and 5 Hz-rTMS (6 for 1Hz-rTMS and 6 for 5Hz-rTMS) administered at 90% MT for 15 min (600 pulses/day) over the left PFC. The assessment was administered after the first and fifth rTMS treatments with the application of the Profile of Mood States, and the HAM-D. The Mississippi Scale of Combat Severity, and the University of Southern California Repeatable Episodic Memory Test were administered after the final rTMS treatment (10 weeks) and at a 1-month and 2-month follow-up. The authors report a significant improvement of hostility, insomnia and anxiety, but only minimal improvements in PTSD symptoms. Seventy-five percent of the patients had a clinically significant antidepressant response after rTMS, and 50% had sustained response at the 2-month follow-up.

Cohen *et al*. [86] administered 10 sessions (5 days per week for 2 weeks) of rTMS to 24 PSTD 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. The group that was treated with 1Hz-rTMS received 100 stimuli per day, in contrast to 10Hz-rTMS and a sham-rTMS group that received 400 stimuli per day. When compared to the other groups, the 10Hz-rTMS group showed improvements of PTSD symptoms (re-experiencing and avoidance) in the PTSD check list and Treatment Outcome for PTSD scale. Also, a significant reduction of general anxiety levels, lasing for 14 days, was observed.

Boggio *et al*. [88] administered 10 sessions (5 days per week for 2 weeks) of rTMS to 30 PSTD patients (20 for rTMS and 10 for 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 severity of core PTSD symptoms, depression, and anxiety were assessed before, during, and after the treatment. In addition, a neuropsychological battery was applied before and after treatment. The authors showed that 20Hz-rTMS applied to both left and right DLPFC as 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 as compared to the left DLPFC. These effects were long lasting and significant at the 3-month follow-up. Moreover, a significant improvement of mood after application of 20Hz-rTMS to the left DLPFC and a significant reduction of anxiety following application to the right DLPFC were reported. The results of the neuropsychological battery indicated that 20Hz-rTMS was not associated with cognitive deterioration and is safe for use in PTSD patients.

The findings above suggest that the positive effect of high frequency of rTMS in the right PFC, particularly in the right DLPFC, may be related to the re-establishment of connectivity between an underactive PFC, which is theorized to mediate amygdala activity and amygdala hyperactivity in PTSD, by increasing PFC activity. Alternatively, the result could be associated with increased activation of the hypothalamic-pituitary-adrenal (HPA) axis, suggesting an association between right prefrontal and HPA axis hypoactivity [86, 88]. Given the effects of rTMS in depression, stimulation in the right PFC with high frequency would then theoretically worsen depressive symptoms that are generally comorbid, since hyperactivity of the HPA axis is commonly implicated in the pathogenesis of depression [102]. The results, in general support the idea that modulation of the right PFC, more specifically the right DLPFC, is capable of reducing PTSD symptoms, suggesting that high-rTMS might be an optimal treatment strategy. The data on PTSD are too preliminary to make an informed decision on the role of rTMS in its treatment, and additional work is needed.

PD

PD is known for recurrent and unexpected attacks of sudden onset and short duration (10-15 min). A panic attack may be followed for up to one month by persistent worry regarding another panic attack. It may consist of several symptoms, such as, feelings of shortness of breath, subsequent hyperventilation, palpitations, chest pain, sweating, chills, nausea, trembling, fear of dying or losing control, numbness, and a feeling of detachment or unreality. Neuroimaging studies have verified that the DLPFC and amygdala are involved in PD [34,103-105].

After extensive search for reliable evidence, only one controlled study was found: Prasko *et al*. [87] administered 10 sessions (5 days per week for 2 weeks) of rTMS to 15 drug-resistant PD patients (7 for Hz-rTMS and 8 for 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 of anxiety symptoms, as verified by the CGI, Panic disorder severity scale (PDSS), HAM-A and Beck anxiety inventory (BAI), however, no

significant differences for PD symptoms were found between the treatment- and sham-groups.

GAD

The main characteristic of GAD is excessive and persistent worry (present for at least 6 months) in various aspects of life (e.g., at work or school performance) or in relation to wellness of family members [16]. Other symptoms include irritability, restlessness and impaired concentration. In addition, somatic symptoms can include muscle tension, sweating, dry mouth, nausea, and diarrhea. Regarding the circuitry of areas involved in GAD, an fMRI study showed that limbic or frontal regions were activated in patients with a high degree of hesitation; the same areas were found to be deactivated when less anxious individuals were exposed to anxiogenic situations [106]. For instance, in a fMRI study, Monk *et al*. [107] demonstrated a strong and negative coupling between right amygdala and right ventrolateral prefrontal cortex (vlPFC) when subjects were asked to respond to angry faces. Similarly, investigations of GAD have demonstrated activation of amygdala, cortex insular bilaterally, limbic and striatal areas, suggesting an involvement on dopaminergic function in the striatal and limbic circuits [16, 108]. conjunção and Ouvir Ler foneticamente .

Based on the idea of an interhemispheric imbalance and/or a deficit in cortico-limbic control as a model for human anxiety, the application of 1Hz-rTMS over prefrontal cortex has demonstrated benefits in PTSD patients [86, 88]. However, no controlled study (sham-rTMS) was performed with GAD patients, which makes it impossible at the moment to make statements about the possible efficiency of TMS against GAD. Bystrisky *et al*. [109] intended to identify in GAD patients a critical area of activation within the prefrontal cortical areas that could be used to target rTMS treatment. The authors administered 6 sessions (2 days per week for 3 weeks) of rTMS to 10 GAD patients, with 1 Hz-rTMS administered at 90% MT for 15 min (900 pulses/day) over the right DLPFC. Patients were rated on the HAM-A, HAM-D, CGI-S and Four-Dimensional Anxiety and Depression Scale, showing a significant reduction in anxiety symptoms on both HAM-A, CGI-S, HAM-D scales.

Investigations regarding the efficacy of rTMS in anxiety disorders have been inclined to look at certain anxiety disorders, such as OCD, PTSD and PD, and have failed to adequately address GAD. In fact, so far there have been no randomized sham-controlled studies of rTMS in GAD patients. The assessment of the efficacy of rTMS in other disorders is vital, since GAD contributes significantly to the high rate of comorbidity between anxiety disorders and depression [110].

SUMMARY AND FUTURE DIRECTIONS

In conclusion, there is yet no conclusive evidence of the efficacy of rTMS as a treatment for anxiety disorders. While positive results have frequently been reported in both open and randomized controlled studies, several treatment parameters, such as location, frequency, intensity and duration, have been used unsystematically, making the interpretation of the results difficult and providing little guidance on what treatment parameters (i.e., stimulus location and frequency) may be the most useful for treating anxiety disorders. Sham-controlled research has often reported symptom improvement in all participants, and has been unable to distinguish between response to rTMS and sham-rTMS treatment [78, 79, 87], indicating that any positive clinical effect may be largely attributed to a placebo effect.

A possible explanation with respect to the efficacy of rTMS in anxiety disorders treatment is limited by the focal nature of the stimulation, with only the superficial cortical layers likely to be directly affected. At present, using available TMS technology, it is not possible to directly stimulate more distant cortical areas, such as OFC, and also subcortical areas, such as amygdala, hippocampus and striatum, which are most likely to be relevant to the pathogenesis of anxiety disorders [3]. Effects in subcortical areas are thought to be indirect, *via* trans-synaptic connections [91]. In addition, the underlying neurobiological disturbance in anxiety disorders may be too diffuse to be easily targeted with TMS technology. Thus, we recommend further studies to clearly determine the role of rTMS in the treatment of anxiety disorders. Finally, it must be remembered that however exciting the neurobiological mechanisms might be, the clinical usefulness of rTMS will be determined by the ability to provide patients with anxiety disorders with safe, long-lasting and substantial improvements in quality of life. Key advances in rTMS and neuroimaging technology may guide and support this aim.

ABREVIATIONS

CGI-S = Clinical Global Impression-Severity of Illness
DLPFC = Dorso lateral prefrontal cortex
EPM = Elevated plus-maze
fMRI = Functional magnetic resonance imaging
GAD = Generalized anxiety disorder
HAM-A = Hamilton Rating Scale for Anxiety
HAM-D = Hamilton Rating Scale for Depression
HPA = Hypothalamic-pituitary-adrenal
L = Left
LTD = Long-term depression
M1 = Primary motor cortex
MEP = Motor evoked potential
ms = Milliseconds
MT = Motor threshold
OCD = Obsessive compulsive disorder
OFC = Orbitofrontal cortex
PD = Panic disorder
PTSD = Posttraumatic stress disorder
R = Right
rTMS = Repetitive transcranial magnetic stimulation
SMA = Supplementary motor area
TMS = Transcranial magnetic stimulation
Y-BOCS = Yale Brown Obsessive Compulsive Scale

REFERENCES

[1] Hill, M.N; Gorzalka, B.B. The endocannabinoid system and the treatment of mood and anxiety disorders. *CNS Neurol. Disord. Drug Targets*, **2009**, *8*, 451-458.
[2] Greenberg, P.E.; Sisitsky, T.; Kessler, R.C.; Finkelstein, S.N.; Berndt, E.R.; Davidson, J.R.; Ballenger, J.C.; Fyer, A.J. The economic burden of anxiety disorders in the 1990s. *J. Clin. Psychiatry*, **1999**, *60*, 427-435.
[3] Resseler, K.J.; Mayberg, H.S. Targeting abnormal neural circuits in mood and anxiety disorders: from the laboratory to the clinic. *Nat. Neurosci.*, **2007**, *10*, 1116-1124.
[4] Barker, A.T.; Jalinous, R.; Freeston, I.L. Non-invasive magneticstimulation of human motor cortex. *Lancet*, **1985**, *1*, 1106-1107.
[5] Tyc, F.; Boyadjian, A. Cortical plasticity and motor activity studied with transcranial magnetic stimulation. *Rev. Neurosci.*, **2006**, *17*, 469-495.
[6] Lai, K.L.; Lin, C.Y.; Liao, K.K.; Wu, Z.A.; Chen, J.T. Transcranial magnetic stimulation after conditioning stimulation in two adrenomyeloneuropathy patients: delayed but facilitated motor-evoked potentials. *Funct. Neurol.*, **2006**, *21*, 141-144.

[7] O´Reardon, J.P.; Peshek, A.D.; Romero Pradilla, R.; Cristancho, P. Neuromodulation and transcranial magnetic stimulation (TMS): a 21st Century paradigm for therapeutics in psychiatry. *Psychiatry*, **2006**, *3*, 30-40.

[8] Hallett, M. Transcranial magnetic stimulation and the human brain. *Nature*, **2000**, *406*, 147-150.

[9] Rossini, P.M.; Rossi S. Transcranial magnetic stimulation: diagnostic, therapeutic, and research potential. *Neurology*, **2007**, *68*, 484-488.

[10] Kim, D.R.; Pesiridou, A.; O'Reardon, J.P. Transcranial magnetic stimulation in the treatment of psychiatric disorders. *Curr. Psychiatry Rep.*, **2009**, *11*, 447-452.

[11] Speer, A.M.; Kimbrell, T.A.; Wassermann, E.M.; Repella, D.J.; Willis, M.W.; Herscovitch, P.; Post, R.M. Oppositive effects of high and low frequency rTMS on regional brain activity in depressed patients. *Biol. Psychiatry*, **2000**, *48*, 1133-1141.

[12] Nahas, Z.; Lomarev, M.; Roberts, D.R.; Shastri, A.; Lorberbaum, J.P.; Teneback, C.; McConnell, K.; Vincent, D.J.; Li, X.; George, M.S.; Bohning, D.E. Unilateral left prefrontal transcranial magnetic stimulation (TMS) produces intensity-dependent bilateral effects as measured by interleaved BOLD fMRI. *Biol. Psychiatry*, **2001**, *50*, 712-720.

[13] Schönfeldt-Lecuona, C.; Cárdenas-Morales, L.; Freudenmann, R.W.; Kammer, T.; Herwig, U. Transcranial magnetic stimulation in depression--lessons from the multicentre trials. *Restor. Neurol. Neurosci.*, **2010**, *28*(4), 569-576.

[14] Höppner, J.; Berger, C.; Walter, U.; Padberg, F.; Buchmann, J.; Herwig, U.; Domes, G. Influence of repetitive transcranial magnetic stimulation on special symptoms in depressed patients. *Restor. Neurol. Neurosci.*, **2010**, *28*(4), 577-586.

[15] Zwanzger, P.; Fallgatter, A.J.; Zavorotnyy, M.; Padberg, F. Anxiolytic effects of transcranial magnetic stimulation-an alternative treatment option in anxiety disorders? *J. Neural Transm.*, **2009**, *116*, 767-775.

[16] Pallanti, S.; Bernardi, S. Neurobiology of repeated transcranial magnetic stimulation in the treatment of anxiety: a critical review. *Int. Clin. Psychopharmacol.*, **2009**, *24*, 163-173.

[17] Hallett, M. Transcranial magnetic stimulation: a primer. *Neuron*, **2007**, *55*, 187-199.

[18] Ziemann, U. TMS induced plasticity in human cortex. *Rev. Neurosci.*, **2004**, *15*, 253-266.

[19] Linden, D.E. What, when, where in the brain? Exploring mental chronometry with brain imaging and electrophysiology. *Rev. Neurosci.*, **2007**, *18*, 159-171.

[20] Bonnard, M.; de Graaf, J.; Pailhous, J. Interactions between cognitive and sensorimotor functions in the motor cortex: evidence from the preparatory motor sets anticipating a perturbation. *Rev. Neurosci.*, **2004**, *15*, 371-382.

[21] Lapitska, N.; Gosseries, O.; Delvaux, V.; Overgaard, M.; Nielsen, F.; Maertens de Noordhout, A.; Moonen, G.; Laureys, S. Transcranial magnetic stimulation in disorders of consciousness. *Rev. Neurosci.*, **2009**, *20*, 235-250.

[22] Pascual-Leone, A.; Walsh, V.; Rothwell, J. Transcranial magnetic stimulation in cognitive neuroscience--virtual lesion, chronometry, and functional connectivity. *Curr. Opin. Neurobiol.*, **2000**, *10*, 232-237.

[23] Thielscher, A.; Kammer, T. Electric field properties of two commercial figure-8 coils in TMS: calculation of focality and efficiency. *Clin. Neurophysiol.*, **2004**, *115*, 1697-1708.

[24] Maeda, F.; Keenan, J.P.; Tormos, J.M.; Topka, H.; Pascual-Leone, A. Interindividual variability of the modulatory effects of repetitive transcranial magnetic stimulation on cortical excitability. *Exp. Brain Res.*, **2000**, *133*, 425-430.

[25] Post, R.M.; Kimbrell, T.; Frye, M.; George, M.; McCann, U.; Little, J.; Dunn, R.; Li, H.; Weiss, S.R.B. Implications for kindling and quenching for the possible frequency dependence of rTMS. *CNS Spectr.*, **1997**, *2*, 54-60.

[26] Hoogendam, J.M.; Ramakers, G.M.; Di Lazzaro, V. Physiology of repetitive transcranial magnetic stimulation of the human brain. *Brain Stimul.*, **2010**, *3*(2), 95-118.

[27] Chen, R.; Classen, J.; Gerloff, C.; Celnik, P.; Wassermann, E.M.; Hallett, M.; Cohen L.G. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. *Neurology,* **1997**, *48*(5), 1398-1403.

[28] Rossini, P.M.; Rossini, L.; Ferreri, F. Brain-behavior relations: transcranial magnetic stimulation: a review. *IEEE Eng. Med. Biol. Mag.*, **2010**, *29*(1), 84-95.

[29] Walsh, V.; Rushworth, M. A primer of magnetic stimulation as a tool for neuropsychology. *Neuropsychologia*, **1999**, *37*, 125-135.

[30] Sparing, R.; Hesse, M.D.; Fink, G.R. Neuronavigation for transcranial magnetic stimulation (TMS): where we are and where we are going. *Cortex*, **2010**, *46*(1), 118-120.

[31] Dileone, M.; Profice, P.; Pilato, F.; Ranieri, F.; Capone, F.; Musumeci, G.; Florio, L.; Di Iorio, R.; Di Lazzaro, V. Repetitive transcranial magnetic stimulation for ALS. *CNS Neurol. Disord. Drug Targets*, **2010**, *9*(3), 331-334.

[32] Pell, G.S.; Roth, Y.; Zangen, A. Modulation of cortical excitability induced by repetitive transcranial magnetic stimulation: Influence of timing and geometrical parameters and underlying mechanisms. *Prog. Neurobiol.*, **2011**, *93*(1), 59-98.

[33] Sachdev, P.; McBride, R.; Loo, C.K.; Mitchell, P. B.; Malhi, G.S.; Croker, V.M. Right versus left prefrontal transcranial magnetic stimulation for obsessive-compulsive disorder: a preliminary investigation. *J. Clin. Psychiatry*, **2001**, *62*, 981-984.

[34] Mayberg, H.S.; Liotti, M.; Brannan, S.K.; McGinnis, S.; Mahurin, R.K.; Jerabek, P.A.; Silva, J.A.; Tekell, J.L.; Martin, C.C.; Lancaster, J.L.; Fox, P.T. Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. *Am. J. Psychiatry*, **1999**, *156*, 675-682.

[35] Garcia-Toro, M.; Salva Coll J.; Crespi Font, M.; Andres Tauler, J.; Aguirre Orue, I.; Bosch Calero, C. Panic disorder and transcranial magnetic stimulation. *Actas Esp. Psiquiatr.*, **2002**, *30*, 221-224.

[36] Post, A.; Keck, M.E. Transcranial magnetic stimulation as a therapeutic tool in psychiatry: what do we know about the neurobiological mechanisms? *J. Psychiatr. Res.*, **2001**, *35*(4), 193-215.

[37] Rossi, S.; Hallett, M.; Rossini, P.M.; Pascual-Leone, A. Safety of TMS Consensus Group. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin. Neurophysiol.*, **2009**, *120*(12), 2008-2039.

[38] Platz, T.; Rothwell, J.C. Brain stimulation and brain repair--rTMS: from animal experiment to clinical trials--what do we know? *Restor. Neurol. Neurosci.*, **2010**, *28*(4), 387-398.

[39] Keck, M.E.; Engelmann, M.; Müller, M.B.; Henniger, M.S.; Hermann, B.; Rupprecht, R.; Neumann, I.D.; Toschi, N.; Landgraf, R.; Post, A. Repetitive transcranial magnetic stimulation induces active coping strategies and attenuates the neuroendocrine stress response in rats. *J. Psychiatr. Res.*, **2000**, *34*(4-5), 265-276.

[40] Kanno, M.; Matsumoto, M.; Togashi, H.; Yoshioka, M., Mano, Y. Effects of repetitive transcranial magnetic stimulation on behavioral and neurochemical changes in rats during an elevated plus-maze test. *J. Neurol. Sci.*, **2003**, *211*, 5-14.

[41] Keck, M.E.; Welt, T.; Post, A.; Muller, M.B.; Toschi, N.; Wigger, A.; Landgraf, R.; Holsboer, F.; Engelmann, M. Neuroendocrine and behavioral effects of repetitive transcranial magnetic stimulation in a psychopathological animal model are suggestive of antidepressant-like effects. *Neuropsychopharmacology*, **2001**, *24*, 337-349.

[42] Hedges, D.W.; Massari, C.; Salyer, D.L.; Lund, T.D.; Hellewell, J.L.; Johnson, A.C.; Lephart, E.D. Duration of transcranial magnetic stimulation effects on the neuroendocrine stress response and coping behavior of adult male rats. *Prog. NeuroPsychopharmacol. Biol. Psychiatry*, **2003**, *27*, 633-638.

[43] Hedges, D.W.; Higginbotham, B.J.; Salyer, D.L.; Lund, T.D. Transcranial magnetic stimulation effects on one-trial learning and response to anxiogenic stimuli in adult male rats. *J. ECT*, **2005**, *21*, 25-30.

[44] Belmaker, R.H.; Grisaru, N. Magnetic stimulation of the brain in animal depression models responsive to ECS. *J. ECT*, **1998**, *14*, 194-205.

[45] Sachdev, P.S.; McBride, R.; Loo, C.; Mitchell, P.M.; Malhi, G.S.; Croker, V. Effects of different frequencies of transcranial magnetic stimulation (TMS) on the forced swim test model of depression in rats. *Biol. Psychiatry*, **2002**, *51*, 474-479.

[46] Wassermannm E.M.; Lisanby, S.H. Therapeutic application of repetitive transcranial magnetic stimulation: a review. *Clin. Neurophysiol.*, **2001**, *112*, 1367-1377.

[47] Weissman, J.D.; Epstein, C.M.; Davey, K.R. Magnetic brain stimulation and brain size: relevance to animal studies. *Electroencephalogr. Clin. Neurophysiol.*, **1992**, *85*, 215-219.

[48] de Graaf, T.A.; Sack, A.T. Null results in TMS: From absence of evidence to evidence of absence. *Neurosci. Biobehav. Rev.*, **2011**, *35*(3), 871-877.

[49] Sandrini, M.; Umiltà, C.; Rusconi, E. The use of transcranial magnetic stimulation in cognitive neuroscience: A new synthesis of methodological issues. *Neurosci. Biobehav. Rev.*, **2011**, *35*(3), 516-536.

[50] Marzi, C.A.; Miniussi, C.; Maravita, A.; Bertolasi, L.; Zanette, G.; Rothwell, J.C.; Sanes, J.N. Transcranial magnetic stimulation selectively impairs interhemi- spheric transfer of visuo-motor information in humans. *Exp. Brain Res.*, **1998**, *118*(3), 435-438.

[51] Dormal, V.; Andres, M.; Pesenti, M. Dissociation of numerosity and duration processing in the left intraparietal sulcus: a transcranial magnetic stimulation study. *Cortex,* **2008**, *44*(4), 462-469.

[52] Knops, A.; Nuerk, H.C.; Sparing, R.; Foltys, H.; Willmes, K. On the functional role of human parietal cortex in number processing: how gender mediates the impact of a 'virtual lesion' induced by rTMS. *Neuropsychologia*, **2006**, *44*(12), 2270-2283.

[53] Sandrini, M.; Rossini, P.M.; Miniussi, C. The differential involvement of inferior parietal lobule in number comparison: an rTMS study. *Neuropsychologia*, **2004**, *42*(14), 1902-1909.

[54] Cappelletti, M.; Barth, H.; Fregni, F.; Spelke, E.S.; Pascual-Leone, A. rTMS over the intraparietal sulcus disrupts numerosity processing. *Exp. Brain Res.*, **2007**, *179*(4), 631-642.

[55] Cohen Kadosh, R.; Cohen Kadosh, K.; Schuhmann, T.; Kaas, A.; Goebel, R.; Henik, A.; Sack, A.T. Virtual dyscalculia induced by parietal-lobe TMS impairs automatic magnitude processing. *Curr. Biol.*, **2007**, *17*(8), 689-693.

[56] Herwig, U.; Cardenas-Morales, L.; Connemann, B.J.; Kammer, T.; Schönfeldt-Lecuona, C. Sham or real-post hoc estimation of stimulation condition in a randomized transcranial magnetic stimulation trial. *Neurosci. Lett.*, **2010**, *471*(1), 30-33.

[57] Lisanby, S.H.; Gutman, D.; Luber, B.; Schroeder, C.; Sackeim, H.A. Sham TMS: intracerebral measurement of the induced electrical field and the induction of motor-evoked potentials. *Biol Psychiatry*, **2001**, *49*(5), 460-463.

[58] Loo, C.K.; Taylor, J.L.; Gandevia, S.C.; McDarmont, B.N.; Mitchell, P.B.; Sachdev, P.S. Transcranial magnetic stimulation (TMS) in controlled treatment studies: are some "sham" forms active? *Biol. Psychiatry*, **2000**, *47*(4), 325-331.

[59] Tsubokawa, T.; Katayama, Y.; Yamamoto, T.; Hirayama, T.; Koyama, S. Chronic motor cortex stimulation in patients with thalamic pain. *J. Neurosurg.,* **1993***, 78*, 393-401.

[60] Shah, D.B.; Weaver, L.; O'Reardon, J.P. Transcranial magnetic stimulation: a device intended for the psychiatrist's office, but what is its future clinical role? *Expert Rev. Med. Devices*, **2008**, *5*(5), 559-566.

[61] O´Reardon, J.P.; Solvason, H.B.; Janicak, P.G.; Sampson, S.; Isenberg, K.E.; Nahas, Z.; McDonald, W.M.; Avery, D.; Fitzgerald, P.B.; Loo, C.; Demitrack, M.A.; George, M.S.; Sackeim, H.A. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multi-site randomized controlled trial. *Biol. Psychiatry*, **2007**, *62*(11), 1208-1216.

[62] Rossi, S.; Ferro, M.; Cincotta, M.; Ulivelli, M.; Bartalini, S.; Miniussi, C.; Giovannelli, F.; Passero, S. A real electro-magnetic placebo (REMP) device for sham transcranial magnetic stimulation (TMS). *Clin. Neurophysiol.*, **2007**, *118*(3), 709-716.

[63] Lisanby, S.H.; Kinnunen, L.H.; Crupain, M.J. Applications of TMS to therapy in psychiatry. *J. Clin. Neurophysiol.*, **2002**, *19*(4), 344-360.

[64] Fitzgerald, P.B.; Benitez, J.; de Castella, A.; Daskalakis, Z.J.; Brown, T.L.; Kulkarni, J. A randomized, controlled trial of sequential bilateral repetitive transcranial magnetic stimulation for treatment-resistant depression. *Am. J. Psychiatry*, **2006**, *163*, 88-94.

[65] Iyer, M.B.; Schelper, N.; Wassermann, E.M. Priming stimulation enhances the depressant effect of low-frequency repetitive transcranial magnetic stimulation. *J. Neurosci.*, **2003**, *23*, 10867-10872.

[66] Huang, Y.Z.; Edwards, M.J.; Rounis, E.; Bhatia, K.P.; Rothwell, J.C. Theta burst stimulation of the human motor cortex. *Neuron,* **2005**, *45*, 201-206.

[67] Tallman, J.F.; Paul, S.M.; Skolnick, P.; Gallager, D.W. Receptor for the age of anxiety: pharmacology of the benzodiazepines. *Science,* **1980***, 207*, 274-281.

[68] Coutinho, F.C.; Dias, G.P.; do Nascimento Bevilaqua, M.C.; Gardino, P.F.; Pimentel Rangé, B.; Nardi, A.E. Current concept of anxiety: implications from Darwin to the DSM-V for the diagnosis of generalized anxiety disorder. *Expert Rev. Neurother.*, **2010**, *10*(8), 1307-1320.

[69] Schutter, D.J.; van Honk, J.; d'Alfonso, A.A.; Postma, A.; de Haan, E.H. Effects of slow rTMS at the right dorsolateral prefrontal cortex on EEG asymmetry and mood. *Neuroreport,* **2001**, *12*, 445-447.

[70] Van Honk, J.; Schutter, D.J.; d'Alfonso, A.A.; Kessels, R.P.; de Haan, E.H. 1 Hz rTMS over the right prefrontal cortex reduces vigilant attention to unmasked but not to masked fearful faces. *Biol. Psychiatry,* **2002**, *52*, 312-317.

[71] Heller, W.; Nitschke, J.B. The puzzle of regional brain activity in depression and anxiety: the importance of subtypes and comorbidity. *Cogn. Emot.,* **1998**, *12*, 421-447.

[72] Hoffman, R.E.; Cavus, I. Slow transcranial magnetic stimulation, long-term depotentiation, and brain hyperexcitability disorders. *Am. J. Psychiatry,* **2002**, *159*, 1093-1102.

[73] George, M.S.; Stallings, L.E.; Speer, A.M.; Nahas, Z.; Spicer, K.M.; Vincent, D.J.; Bohning, D.E.; Cheng, K.T.; Molloy, M.; Teneback, C.C.; Risch, S.C. Prefrontal repetitive transcranial magnetic stimulation (rTMS) changes relative perfusion locally and remotely. *Hum. Psychopharmacol. Clin. Exp.*, **1999**, *14*(3), 161-170.

[74] Pena-Garijo, J.; Ruipérez-Rodríguez, M.A.; Barros-Loscertales, A. The neurobiology of obsessive-compulsive disorder: new findings from functional magnetic resonance imaging (I). *Rev. Neurol.,* **2010**, *50*(8), 477-485.

[75] Pena-Garijo, J.; Ruipérez-Rodríguez, M.A.; Barros-Loscertales, A. The neurobiology of obsessive-compulsive disorder: new findings from functional magnetic resonance imaging (II). *Rev. Neurol.,* **2010**, *50*(9), 541-550.

[76] Saxena, S.; Brody, A.L.; Ho, M.L.; Alborzian, S.; Maidment, K.M.; Zohrabi, N.; Ho, M.K.; Huang, S.C.; Wu, H.M.; Baxter, L.R., Jr. Differential cerebral metabolic changes with paroxetine treatment of obsessive-compulsive disorder *vs* major depression. *Arch. Gen. Psychiatry,* **2002**, *59*(3), 250-261.

[77] Alonso, P.; Pujol, J.; Cardoner, N.; Benlloch, L.; Deus, J.; Menchón, J.M.; Capdevila, A.; Vallejo, J. Right prefrontal repetitive transcranial magnetic stimulation in obsessive-compulsive disorder: a double-blind, placebo-controlled study. *Am. J. Psychiatry,* **2001**, *158*(7), 1143-1145.

[78] Prasko, J.; Pasková, B.; Záleský, R.; Novák, T.; Kopecek, M.; Bares, M.; Horácek, J. The effect of repetitive transcranial magnetic stimulation (rTMS) on symptoms in obsessive compulsive disorder. A randomized, double blind, sham controlled study. *Neuro. Endocrinol. Lett.,* **2006**, *27*(3), 327-332.

[79] Sachdev, P.S.; Loo, C.K.; Mitchell, P.B.; McFarquhar, T.F.; Malhi, G.S. Repetitive transcranial magnetic stimulation for the treatment of obsessive compulsive disorder: a double-blind controlled investigation. *Psychol. Med.,* **2007**, *37*(11), 1645-1649.

[80] Kang, J.I.; Kim, C.H.; Namkoong, K.; Lee, C.I.; Kim, S.J. A randomized controlled study of sequentially applied repetitive transcranial magnetic stimulation in obsessive-compulsive disorder. *J. Clin. Psychiatry,* **2009**, *70*(12), 1645-1651.

[81] Ruffini, C.; Locatelli, M.; Lucca, A.; Benedetti, F.; Insacco, C.; Smeraldi, E. Augmentation effect of repetitive transcranial magnetic stimulation over the orbitofrontal cortex in drug-resistant obsessive-compulsive disorder patients: a controlled investigation. *Prim. Care Companion J. Clin. Psychiatry,* **2009**, *11*(5), 226-230.

[82] Mantovani, A.; Simpson, H.B.; Fallon, B.A.; Rossi, S.; Lisanby, S.H. Randomized sham-controlled trial of repetitive transcranial magnetic stimulation in treatment-resistant obsessive-compulsive disorder. *Int. J. Neuropsychopharmacol.,* **2010**, *13*(2), 217-227.

[83] Sarkhel, S.; Sinha, V.K.; Praharaj, S.K. Adjunctive high-frequency right prefrontal repetitive transcranial magnetic stimulation (rTMS) was not effective in obsessive-compulsive disorder but improved secondary depression. *J. Anxiety Disord.,* **2010**, *24*(5), 535-539.

[84] Greenberg, B.D.; Ziemann, U.; Harmon, A.; Murphy, D.L.; Wassermann, E.M. Decreased neuronal inhibition in cerebral cortex in obsessive-compulsive disorder on transcranial magnetic stimulation. *Lancet,* **1998**, *352*(9131), 881-882.

[85] Mantovani, A.; Lisanby, S.H.; Pieraccini, F.; Ulivelli, M.; Castrogiovanni, P.; Rossi, S. Repetitive transcranial magnetic stimulation (rTMS) in the treatment of obsessive-compulsive disorder (OCD) and Tourette's syndrome (TS). *Int. J. Neuropsychopharmacol.,* **2006**, *9*(1), 95-100.

[86] Cohen, H.; Kaplan, Z.; Kotler, M.; Kouperman, I.; Moisa, R.; Grisaru, N. Repetitive transcranial magnetic stimulation of the right dorsolateral prefrontal cortex in posttraumatic stress disorder: a double-blind, placebo-controlled study. *Am. J. Psychiatry,* **2004**, *161*(3), 515-524.

[87] Prasko, J.; Záleský, R.; Bares, M.; Horácek, J.; Kopecek, M.; Novák, T.; Pasková, B. The effect of repetitive transcranial magnetic stimulation (rTMS) add on serotonin reuptake inhibitors in patients with panic disorder: a randomized, double blind sham controlled study. *Neuro. Endocrinol. Lett.,* **2007**, *28*(1), 33-38.

[88] Boggio, P.S.; Rocha, M.; Oliveira, M.O.; Fecteau, S.; Cohen, R.B.; Campanhã, C.; Ferreira-Santos, E.; Meleiro, A.; Corchs, F.; Zaghi, S.; Pascual-Leone, A.; Fregni, F. Noninvasive brain stimulation with high-frequency and low-intensity repetitive transcranial magnetic stimulation treatment for posttraumatic stress disorder. *J. Clin. Psychiatry,* **2010**, *71*(8), 992-999.

[89] Herrmann, L.L.; Ebmeier, K.P. Factors modifying the efficacy of transcranial magnetic stimulation in the treatment of depression: a review. *J. Clin. Psychiatry,* **2006**, *67*(12), 1870-1876.

[90] Abramowitz, J.S.; Storch, E.A.; Keeley, M.; Cordell, E. Obsessive-compulsive disorder with comorbid major depression: what is the role of cognitive factors? *Behav. Res. Ther.,* **2007**, *45*(10), 2257-2267.

[91] George, M.S.; Wassermann, E.M.; Post, R.M. Transcranial magnetic stimulation: a neuropsychiatric tool for the 21st century. *J. Neuropsychiatry Clin. Neurosci.,* **1996**, *8*(4), 373-382.

[92] Shin, L.M.; Rauch, S.L.; Pitman, R.K. Amygdala, medial prefrontal cortex, and hippocampal function in PTSD. *Ann. NY Acad. Sci.,* **2006**, *1071*, 67-79.

[93] Bremner, J.D. Neuroimaging studies in post-traumatic stress disorder. *Curr. Psychiatry Rep.,* **2002**, *4*(4), 254-263.

[94] Bremner, J.D. Brain imaging in anxiety disorders. *Expert Rev. Neurother.,* **2004**, *4*(2), 275-284.

[95] Bremner, J.D. Effects of traumatic stress on brain structure and function: relevance to early responses to trauma. *J. Trauma Dissociation,* **2005**, *6*(2), 51-68.

[96] Bremner, J.D. Stress and brain atrophy. *CNS Neurol. Disord. Drug Targets,* **2006**, *5*(5), 503-512.

[97] Jatzko, A.; Schmitt, A.; Kordon, A.; Braus, D.F. Neuroimaging findings in posttraumatic stress disorder: review of the literature. *Fortschr. Neurol. Psychiatry,* **2005**, *73*(7), 377-391.

[98] Ferrari, M.C.; Busatto, G.F.; McGuire, P.K.; Crippa, J.A. Structural magnetic resonance imaging in anxiety disorders: an update of research findings. *Rev. Bras. Psiquiatr.,* **2008**, *30*(3), 251-264.

[99] Pigot, M.; Loo, C.; Sachdev, P. Repetitive transcranial magnetic stimulation as treatment for anxiety disorders. *Expert Rev. Neurother.,* **2008**, *8*(10), 1449-1455.

[100] Grisaru, N.; Amir, M.; Cohen, H.; Kaplan, Z. Effect of Transcranial Magnetic Stimulation in Posttraumatic Stress Disorder: A preliminary study. *Biol. Psychiatry*, **1998**, *44*, 52–55.

[101] Rosenberg, P.B.; Mehndiratta, R.B.; Mehndiratta, Y.P.; Wamer, A.; Rosse, R.B.; Balish, M. Repetitive transcranial magnetic stimulation treatment of comorbid posttraumatic stress disorder and major depression. *J. Neuropsychiatry Clin. Neurosci.,* **2002**, *14*(3), 270-276.

[102] Thomson, F.; Craighead, M. Innovative approaches for the treatment of depression: targeting the HPA axis. *Neurochem. Res.,* **2008**, *33*(4), 691-707.

[103] van den Heuvel, O.A.; Veltman, D.J.; Groenewegen, H.J.; Witter, M.P.; Merkelbach, J.; Cath, D.C.; van Balkom, A.J.; van Oppen, P.; van Dyck, R. Disorder-specific neuroanatomical correlates of attentional bias in obsessive-compulsive disorder, panic disorder, and hypochondriasis. *Arch. Gen. Psychiatry,* **2005**, *62*, 922-933.

[104] Nordahl, T.E.; Stein, M.B.; Benkelfat, C.; Andreason, P.; Zametkin, A.; Uhde, T.W.; Cohen, R.M. Regional cerebral metabolic asymmetries replicated in an independent group of patients with panic disorders. *Biol. Psychiatry,* **1998**, *44*, 998-1006.

[105] Prasko, J.; Horacek, J.; Zalesky, R.; Kopecek, M.; Novak, T.; Paskova, B.; Skrdlantova, L.; Belohlavek, O.; Hoschl, C. The change of regional brain metabolism (18FDGPET) in panic disorder during the treatment with cognitive behavioral therapy or antidepressants. *Neuro. Endocrinol. Lett.,* **2004**, *25*, 340-348.

[106] Krain, A.L.; Gotimer, K.; Hefton, S.; Ernst, M.; Castellanos, F.X.; Pine, D.S.; Milham, M.P. A functional magnetic resonance imaging investigation of uncertainty in adolescents with anxiety disorders. *Biol. Psychiatry,* **2008**, *63*(6), 563-568.

[107] Monk, C.S.; Telzer, E.H.; Mogg, K.; Bradley, B.P.; Mai, X.; Louro, H.M.; Chen, G.; McClure-Tone, E.B.; Ernst, M.; Pine, D.S. Amygdala and ventrolateral prefrontal cortex activation to masked angry faces in children and adolescents with generalized anxiety disorder. *Arch. Gen. Psychiatry,* **2008**, *65*(5), 568-576.

[108] Damsa, C.; Kosel, M.; Moussally, J. Current status of brain imaging in anxiety disorders. *Curr. Opin. Psychiatry,* **2009**, *22*(1), 96-110.

[109] Bystritsky, A.; Kaplan, J.T.; Feusner, J.D.; Kerwin, L.E.; Wadekar, M.; Burock, M.; Wu, A.D.; Iacoboni, M. A preliminary study of fMRI-guided rTMS in the treatment of generalized anxiety disorder. *J. Clin. Psychiatry,* **2008**, *69*(7), 1092-1098.

[110] Gorman, J.M. Comorbid depression and anxiety spectrum disorders. *Depress. Anxiety,* **1996-1997**, *4*(4), 160-168.

Received: November 28, 2010 **Revised: January 26, 2011** **Accepted: January 27, 2011**