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Review

Is rTMS an effective therapeutic strategy that can be used to treat anxiety disorders?

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ABSTRACT

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive procedure whereby a pulsed magnetic field stimulates electrical activity in the brain. Anxiety disorders are the most common of all mental health problems for which effective, mechanism-based treatments remain elusive. Consequently, more advanced non-invasive therapeutic methods are required. A possible method to modulate brain activity and potentially viable for use in clinical practice is rTMS. Here, we focus on the main findings of rTMS from animal models of anxiety and the experimental advances of rTMS that may become a viable clinical application to treat anxiety disorders, one of the most common causes of disability in the workplace in the world. Key advances in combining rTMS with neuroimaging technology may aid such future developments.

This article is part of a Special Issue entitled 'Anxiety and Depression'.

1. Introduction

Anxiety disorders, as a group of psychiatric disorders, are the most common mental illnesses in the world (Hill and Gorzalka, 2009). In the United States the lifetime prevalence of anxiety disorders is about 29% (Kessler et al., 2005). Anxiety disorders subsume obsessive-compulsive disorder (OCD), panic disorder (PD), post-traumatic stress disorder (PTSD), generalized anxiety disorder (GAD) and social anxiety disorder (SAD). 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 (Ressler and Mayberg, 2007). With advances in the understanding the neurobiological mechanisms involved in anxiety disorders, new treatments have been espoused. One such treatment method used is transcranial magnetic stimulation (TMS), originally introduced in 1985 as a method for non-invasive focal brain stimulation (Barker et al., 1985). 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 (Tyc and Boyadjian, 2006).

Though used increasingly for some neurological and psychiatric disorders, the use of rTMS for anxiety disorders is less well-established. Because of its potential for interfering with cortical function and for inducing plastic changes, rTMS has been widely evaluated as a therapeutic tool in several neuropsychiatric disorders. 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 (Hallett, 2000; Kim et al., 2009; Rossini and Rossi, 2007). Within this context, the use of rTMS is considered a brain-system-based neuromodulation treatment due to its focus on directly targeting the neural circuitry of the disorders (Fig. 1a). rTMS acts altering or modulating the function of the neural

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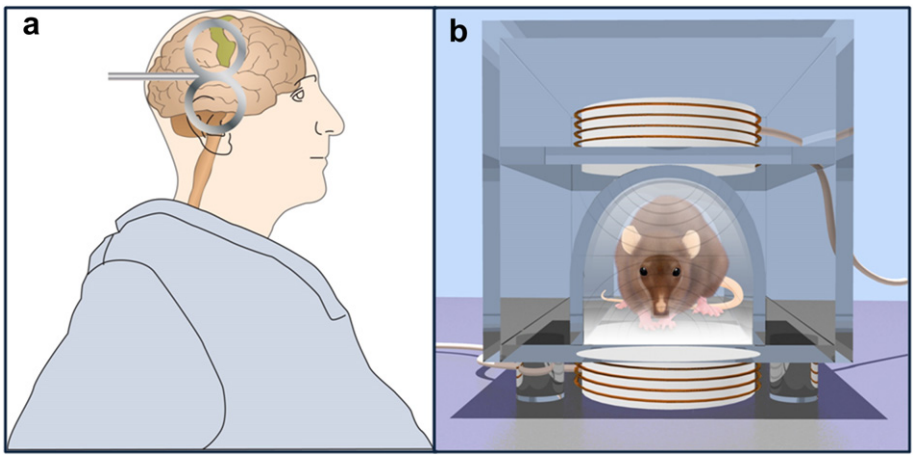

Fig. 1. Repetitive transcranial magnetic stimulation (rTMS) in humans and rodents. According to the evidence cited in this review, there are basically two types of coils: round coils which are relatively non focal and figure-of-eight-shaped coils used to stimulate specific areas, producing maximal current at the intersection of the two round components. The modulatory effects of rTMS depend particularly on the intensity, frequency, train length, inter-train interval, total number of magnetic pulses delivered in the stimulation session, as well as on the coil configuration, current direction, pulse waveform and position of the coil with respect to the cortex. a) In humans, the area of stimulation depends on the shape of the coil and the stimulation intensity. b) The problem of the ratio of coil size to head size in animal rTMS studies. Due to the limitations in coil design, coils used to stimulate animal brains are disproportionately large relative to human coils.

circuitry in the brain that is believed to be disorganized in certain disorders (Nahas et al., 2001; Speer et al., 2000). In fact, there is now a growing interest in the research of new treatment for anxiety disorders; however, the main focus of the possible therapeutic effects of rTMS is still in the domain of depression (Höppner et al., 2010; Schonfeldt-Lecuona et al., 2010). Thus, 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 basic foundation of rTMS, the main findings of rTMS from animal models of anxiety and the experimental advances of rTMS that can become viable as clinical applications in the coming years related to the treatment of anxiety disorders.

2. Basic foundation of repetitive transcranial magnetic stimulation (rTMS)

rTMS is the application to a certain brain area of a train of repeated TMS pulses with the same intensity at a given frequency (Hallett, 2000, 2007). TMS was originally introduced by Anthony Barker in 1985 as non-invasive focal brain stimulation, safe and painless way to study the CNS, more specifically to activate human motor cortex and to assess the human central motor pathways (Barker et al., 1985). Transcranial magnetic stimulation exploits the principle of inductance discovered by Michael Faraday in 1838 (i.e., Faraday's law of electromagnetic induction) where an electrical current is applied over the scalp and skull in order to transmit electrical energy 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. 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. Stimulation is delivered in trains, lasting several seconds, followed by inter-train intervals. The maximal field strength generated by commercially available stimulators is in the 2 T range and they 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 supposed that the magnetic stimulus (duration of ~100 μs) synchronously excites a population of neurons, inducing rapid changes in the firing rates of certain neural networks during only a few milliseconds (Pascual-Leone et al., 2000). The time-varying magnetic field induces a weak and short-lived current, flowing in loops parallel to the orientation of the coil, at the site of stimulation that results in neuronal depolarization or spiking. The magnitude of the induced current is dependent on both the magnitude and rate of change of the current discharged through the coil.

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 (Lai et al., 2006; O'Reardon et al., 2006). 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 (Maeda et al., 2000), high-frequency rTMS seems to facilitate cortical excitability, while low-frequency rTMS can suppress this excitability on the motor cortex (Chen et al., 1997; Pascual-Leone et al., 1994). Recently, a novel pattern of rTMS called theta-burst stimulation (TBS) was developed to produce changes in the human cerebral cortex excitability (Huang et al., 2005). The main advantage of TBS paradigm as 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., 2005 proposed a TBS protocol consisting of bursts of 3 pulses given at 50 Hz repeated every 200 ms (5 Hz), thus, mimicking the coupling of theta and gamma rhythms in the brain (Huang et al., 2005). Two main modalities of TBS have been tested. Intermittent TBS (iTBS) induces facilitation of motor cortical excitability whereas continuous TBS (cTBS) leads to inhibition for 15–30 min after application (Cardenas-Morales et al., 2010; Huang et al., 2005).

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) measured with relaxed muscles. It is defined as the minimum amount of energy (i.e., intensity of stimulation) needed to induce a MEP in a hand muscle in at least 5 out of 10

consecutive trials (Rossini et al., 1994, 2010). RMT is additionally used to establish the individual intensity of stimulation, usually described as a percentage of the device's available output (Walsh and Rushworth, 1999).

In addition, other important considerations to be taken into account, in order to optimize the clinical effects of rTMS, are the parameters of stimulation, e.g., pulse width, number of stimulation sessions, intensity, site of stimulation and frequency (Dileone et al., 2010). For instance, lower frequencies of rTMS, in the 1 Hz range, can suppress the excitability of the motor cortex, while 20 Hz stimulation trains seem to lead to a temporary increase in cortical excitability (Paes et al., 2011). 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 to other cortical regions to study brain–behavior relations. Instead, 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 (Paes et al., 2011).

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 (de Graaf and Sack, 2011), such as the most common strategy used, sham stimulation (sham-rTMS) (Sandrini et al., 2011). Careful consideration of cortical targets seems to be critical, and this 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, seems to be a crucial procedure to adopt (de Graaf and Sack, 2011; Sandrini et al., 2011).

3. Factors influencing the individual response to rTMS

During the last years, genetic diversity in human population has been a crucial topic in clinical research. It has been hypothesized that common genetic variants may contribute to genetic risk for some diseases and that they might influence the subject's response to TMS (Cheeran et al., 2008; Kleim et al., 2006). One could speculate that a profound knowledge on genetic variants might help to predict whether participants will respond or not to magnetic stimulation and in which direction the modulation will take place.

The Brain Derived Neurotrophic Factor (BDNF) gene has been associated to the individual response to rTMS. This gene has 13 exons and it 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 this SNP though located in the pro-BDNF alters intracellular processing and secretion of BDNF (Egan et al., 2003). In healthy subjects it has been associated with mild memory impairments, reduction in hippocampal and frontal cortical areas and some personality traits (Egan et al., 2003). This Val66Met polymorphism could be also associated to psychiatric disorders such as depression and risk of schizophrenia, as well as to the pathogenesis of some neurodegenerative diseases, i.e., Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis (Egan et al., 2003).

The strong evidence, on the one hand, of a functional role for this BDNF common polymorphism, and on the other hand, the implication of this gene 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 demonstrated that the facilitation following the performance of fine-motor tasks, reflected as an increase in the amplitude of cMAPs, was more pronounced in Val/Val polymorphism carriers as compared to Val/Met or Met/Met carriers (Kleim et al., 2006). A second 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 as compared to those subjects with Val66Val polymorphism (Cheeran et al., 2008).

Beside genetic variations a second factor influences the individual response to TMS: the physiological state of neurons at the time of stimulation. Synaptic plasticity can be modulated by prior synaptic activity. The direction and the degree of modulation seem to depend on the previous state of the network. This kind of plasticity is called metaplasticity (Abraham and Bear, 1996; Turrigiano et al., 1998). 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. In animal models, it has been related to the NMDA-receptor activation, Ca^{+2} influx, CaM, CaMKII and to modifications of inhibition of GABA release (Davies et al., 1991).

The phenomenon of metaplasticity has been demonstrated applying rTMS at cortical regions that have previously been modulated by means of cathodal or anodal transcranial direct current stimulation (Siebner et al., 2004). 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 hold 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 than 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.

4. Potential cellular and molecular mechanisms of rTMS in animal models of anxiety disorders

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 (Pallanti and Bernardi, 2009; Zwanzger et al., 2009), instead of preliminary studies using rTMS have provided largely inconclusive evidence of symptom relief in obsessive-compulsive disorder (Sachdev et al., 2001) and panic disorder (Mayberg et al., 1999). 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 (Zwanzger et al., 2009). 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 (Pallanti and Bernardi, 2009; Post and Keck, 2001; Rossi et al., 2009). Within this context, the limitations of human research require appropriate pre-clinical studies in animal models (Arias-Carrión, 2008; Platz and Rothwell, 2010). 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 (Arias-Carrión, 2008; Platz and Rothwell, 2010).

In animal studies, rTMS has been reported to improve some anxiety-related behaviors (Kanno et al., 2003; Keck et al., 2000). An experiment demonstrated that the intensity of stimulation is a critical factor in the anxiolytic benefit as assessed by the elevated plus-maze (EPM) test in male Wistar rats (Kanno et al., 2003). The chronic rTMS treatment, i.e., 5 trains of 25 Hz-rTMS for 1 s (125 pulses/day) with 2 min intervals between trains per 3 days, induced rats to execute EPM test better than rats exposed to acute rTMS treatment at the same conditions per 1 day, and in addition 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 effects in rats, which are related to the 5-HTergic neuronal system. On the other hand, other studies have been reported that chronic rTMS treatment with 3 trains of 20 Hz-rTMS for 2.5 s (150 pulses/day) at 130% of rat's MT daily for 8 weeks, 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 (Keck et al., 2000, 2001). However, other experiments contradicted the findings, showing no differences on the performance of the same task between animals treated by 15 Hz-rTMS at 80% rat's MT for 3 s for 10 consecutive days and sham-TMS (Hedges et al., 2005, 2003). Last but not least, Hargreaves et al. (2005) administered 18 days of 4 trains of 20 Hz-rTMS daily for 4 s (320 pulses/day) with an inter-train interval of 30 s to male Sprague-Dawley rats. The authors showed that no significant differences were found in any of the anxiety models examined, such as, social interaction, emergence, elevated plus-maze, and predator odor avoidance, while active-rTMS compared to sham-rTMS produced a modest, but not significant, antidepressant-like activity in the forced swim test. In this task, Hargreaves and colleagues did not find an increased swimming behavior compared to sham-treated rats, suggesting that the level of stress observed during the task performance may have accompanied sham-treatment.

In general, results from animal models of anxiety-related disorders have demonstrated an antidepressant-like activity of rTMS with some consistency. For instance, in studies using the forced swim test (the most widely used pre-clinical antidepressant test), rTMS demonstrated a robust treatment-induced antidepressant-like activity in rodent models of anxiety (Belmaker and Grisaru, 1998; Hedges et al., 2003; Keck et al., 2000; Sachdev et al., 2002). 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 (Hedges et al., 2005).

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 (Fig. 1b). Because of this and other limitations, e.g., stress associated with 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 (Wassermann and Lisanby, 2001). 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 (Weissman et al., 1992).

5. rTMS effects on anxiety disorders in humans

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 object directed at it, such as an irrational dread of routine stimuli, it becomes a disabling disorder and is considered to be pathological (Coutinho et al., 2010; Tallman et al., 1980). The term "anxiety disorders" subsumes a wide variety of conditions of abnormal and pathological fear and anxiety, including OCD, PTSD, PD, GAD and SAD (Pallanti and Bernardi, 2009; Zwanzger et al., 2009). The anxiety disorders comprise the most frequent psychiatric disorders and can range from relatively beginning feelings of nervousness to extreme expressions of terror and fear.

Based on the idea of an interhemispheric imbalance and/or deficit in the limbic-cortico control, (Ressler and Mayberg, 2007) proposed a model for human anxiety based on the theory so called "valence-hypothesis", which has been formerly proposed for (Heller et al., 1997). According to this model, withdrawal-related emotions such as anxiety are located to the right hemisphere, whereas approach related emotions such as joy or happiness are biased to the left hemisphere. In line with this hypothesis, Keller et al. (2000) examined and found an increased right–hemispheric activity in anxiety disorders, reinforcing an association between increased right–hemispheric activity and anxiety. The first evidence of this model was observed by the use of 1 Hz-rTMS on the right prefrontal cortex (PFC) has demonstrated effects in some studies involving healthy individuals (Zwanzger et al., 2009). However, Pallanti and Bernardi also argued that rTMS over the left dorsolateral prefrontal cortex (DLPFC), especially above 5 Hz-rTMS, reduces the symptoms of anxiety in PTSD and panic disorders (Pallanti and Bernardi, 2009). Therefore, to further elucidate the putative anxiolytic action of rTMS in anxiety patients future studies have to be conducted.

Other studies set out to investigate the hypothesis of high-rTMS efficacy in anxiety disorders treatment (Pallanti and Bernardi, 2009). Specifically, the cerebral hyperexcitability and behavioral or cognitive activation observed in neuropsychiatric disorders support this hypothesis (Hoffman and Cavus, 2002). The studies 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 (George et al., 1996; Pallanti and Bernardi, 2009). In this section, we will discuss the mechanisms and circuitries involved in anxiety disorders (i.e., OCD, PTSD, PD and GAD) and the therapeutic effects of rTMS for each disorder. Moreover, we will give a brief description and present the main findings of rTMS treatment for each disorder (see Table 1).

5.1. Obsessive-compulsive disorder (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 (Coutinho et al., 2010).

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

Study OCD	Design	*N*	rTMS protocol	Efficacy
Greenberg et al., 1998	Open study 1 session	12	PFC–R 20 Hz of 80% MT PFC–L 20 Hz of 80% MT Occipital 20 Hz 80% MT	Reduction in OCD symptoms only with right-sided treatment.[a]
Sachdev et al., 2001	Open study 10 sessions (5 days per week for 2 weeks)	12	PFC–R 10 Hz of 110% MT PFC–L 10 Hz of 110% MT	Both groups showed a significant reduction in OCD symptoms.[a] 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 1 Hz of 110% MT Sham-rTMS	Slight reduction in OCD symptoms in rTMS group.[a] 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 1 Hz of 100% MT	Significant reduction in OCD symptoms.[a]
Prasko et al., 2006	RCT 10 sessions (5 days per week for 2 weeks)	30	DLPFC–L 1 Hz of 110% MT Sham-rTMS	Both groups showed a significant reduction in anxiety.[a] 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 10 Hz of 110% MT Sham-rTMS	No significant difference was found between groups. However, after comparison, all subjects 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 1 Hz of 100% MT Sham-rTMS	No significant difference was found on both groups and between groups.
Ruffini et al., 2009	RCT 15 sessions (5 days per week for 3 weeks)	23	OFC–L 1 Hz of 80% MT Sham-rTMS	Significant reduction in OCD symptoms in favor of rTMS compared to sham-rTMS.[a] 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 1 Hz of 100% MT Sham-rTMS	Significant reduction in OCD symptoms in favor of rTMS compared to sham-rTMS.[a]
Sarkhel et al., 2010	RCT 10 sessions (5 days per week for 2 weeks)	42	PFC–R 10 Hz of 110% MT Sham-rTMS	Significant reduction in OCD symptoms and a significant improvement in mood in both groups.[a] 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.[a]
Rosenberg et al., 2002	Open study 10 sessions (5 days per week for 2 weeks)	12	DLPFC–L 1 Hz of 90% MT DLPFC–L 5 Hz of 90% MT	Significant improvement of insomnia, hostility and anxiety, but minimal improvements in PTSD symptoms.[a] However, no significant different was noted between groups.
Cohen et al., 2004	RCT 10 sessions (5 days per week for 2 weeks)	24	DLPFC–R 1 Hz of 80% MT DLPFC–R 10 Hz of 80% MT Sham-rTMS	Significant improvement of PTSD symptoms and a significant reduction in general anxiety levels in favor of 10 Hz-rTMS group when compared to other groups.[a]
Boggio et al., 2010	RCT 10 sessions (5 days per week for 2 weeks)	30	DLPFC–L 20 Hz of 80% MT DLPFC–R 20 Hz of 80% MT Sham-rTMS	Significant reduction in PTSD symptoms, anxiety and improvement of mood in favor of rTMS compared to sham-rTMS.[a]
PD				
Prasko et al., 2007	RCT 10 sessions (5 days per week for 2 weeks)	15	DLPFC–R 1 Hz of 110% MT Sham-rTMS	Both groups showed a significant reduction in anxiety symptoms.[a] However, no significant difference was found between groups for PD symptoms.
GAD				
Bystritsky et al., 2009	Open study 6 sessions (2 days per week for 3 weeks)	10	DLPFC–R 1 Hz of 90% MT	Significant reduction in anxiety symptoms.[a]

DLPFC: dorsolateral prefrontal cortex; L: left; GAD: generalized anxiety disorder; MT: motor threshold; OCD: obsessive-compulsive disorder; PD: panic disorder; PTSD: post-traumatic stress disorder; R: right; RCT: randomized clinical trial; rTMS: repetitive transcranial magnetic stimulation; SMA: supplementary motor area.
[a] Significant level at ≤ 0.05.

With regard to the brain circuits involved in OCD, several studies had detected abnormalities involving mainly cortical and sub-cortical structures, such as the basal ganglia, orbitofrontal cortex (OFC), supplementary motor area (SMA), DLPFC, and in particular, the caudate nucleus (Pena-Garijo et al., 2010a,b). 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 (Saxena et al., 2002).

Within this context, a few reliable studies related to treatment of OCD symptoms were performed. Eight randomized controlled studies (i.e., using sham-coil) investigated the efficacy of rTMS on the reduction of OCD symptoms (Alonso et al., 2001; Kang et al., 2009; Mantovani et al., 2010; Prasko et al., 2006; Rossini et al., 2010; Sachdev et al., 2007; Sarkhel et al., 2010). However, only few studies reported significant differences between active-rTMS and sham-rTMS for OCD symptoms (Mantovani et al., 2010; Sarkhel et al., 2010). In addition to these studies, another 3 non-controlled studies to investigate rTMS effects on OCD symptoms, reporting no significant differences between active-rTMS and sham-rTMS (Greenberg et al., 1998; Mantovani et al., 2006; Sachdev et al., 2001).

With respect to non-controlled studies, in an intra-individual crossover study, Greenberg et al. 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 (OCC) on separate days (Greenberg et al., 1998). Compulsive symptoms improved until 8 h after rTMS application over the right PFC as rated on Yale Brown Obsessive Compulsive Scale (Y-BOCS). However, application of rTMS to the left PFC resulted in a shorter-lasting

(i.e., 30 min) and non-significant reduction in compulsive symptoms. Moreover, mood improved during and 30 min after rTMS application over the right PFC as rated on Hamilton Rating Scale for Depression (HAM-D). Compulsive symptoms also improved after rTMS applied to the OCC, although not significantly.

In open study, Sachdev et al. 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 ($n = 6$). 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 (Sachdev et al., 2001). 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 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 SMA (Mantovani et al., 2006). After the second week of treatment, statistically significant reductions were still detected with the Y-BOCS and other scales. Symptom improvement was correlated with a significant increase of the right resting motor threshold and was stable at 3-month follow-up. 1 Hz-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. 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 (Alonso et al., 2001). 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 and total scores of Y-BOCS and HAM-D. Similarly, Prasko et al. 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 (Prasko et al., 2006). 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. 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 (Sachdev et al., 2007). 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. 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 SMA (Kang et al., 2009). There were no significant differences over 4 weeks between the rTMS and sham-rTMS groups on the Y-BOCS and the MADRS. These findings suggest that 10 sessions of sequential rTMS of the right DLPFC and the SMA at 1 Hz-rTMS had no therapeutic effect on OCD symptoms.

Ruffini et al. 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 (Ruffini et al., 2009). 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 1 Hz-rTMS applied to the left OFC produced a significant but time-limited improvement in the OCD patients.

Mantovani et al. 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 (Mantovani et al., 2010). 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. 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 (Sarkhel et al., 2010). They reported a significant reduction in OCD symptoms and a significant improvement in mood in both rTMS and sham-rTMS groups. However, the 10 Hz-rTMS treatment was not superior to sham-rTMS according to the Y-BOCS scores. The authors concluded that 10 Hz-rTMS applied to right PFC did not have significant effect in the treatment of OCD, but, that, 10 Hz-rTMS was modestly effective in the treatment of comorbid depressive symptoms in the patients with OCD.

At last, Mansur et al. applied 30 sessions (5 days per week for 6 weeks) of rTMS to 30 OCD patients with 10 Hz-rTMS (15 for rTMS and 15 for sham-rTMS) administered at 110% MT for 20 min over the right DLPFC (Mansur et al., 2011). The authors found positive responses in Y-BOCS (30% of improvement) and in CGI ('much improved' or 'very much improved'). Thus, they concluded that 10 Hz-rTMS treatment over the rDLPFC was not superior to sham-rTMS in relieving OCD symptoms, reducing clinical severity, or improving treatment response.

More recently, in a meta-analysis, Slotema et al. concluded and do explicitly not recommend rTMS for the treatment of OCD (Slotema et al., 2010). However, in this study, the authors found only 3 randomized-controlled trials, in contrast to the studies of Pigot et al. that showed a few positive effects of rTMS for OCD (Pigot et al., 2008).

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 (Mantovani et al., 2010; Ruffini et al., 2009). 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 three studies assessed the effects of rTMS compared to sham-rTMS over at least 4 weeks (Alonso et al., 2001; Mantovani et al., 2010). However, rTMS was only given three-times per week

(Alonso et al., 2001), in contrast to the second and third studies that administered rTMS five-times per week (Mantovani et al., 2010).

At least 2 studies may have been underpowered, suggesting that results may be attributed to a type II error (Alonso et al., 2001; Prasko et al., 2006). The low placebo response reported in OCD patients supports this suspicion. However, Sachdev et al. noted that given the effect size in their study, a very large sample would have been required to demonstrate a group difference (Sachdev et al., 2007). 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) (Alonso et al., 2001; Boggio et al., 2010; Cohen et al., 2004; Kang et al., 2009; Mantovani et al., 2006, 2010; Prasko et al., 2006; Prasko et al., 2007; Ruffini et al., 2009; Sachdev et al., 2007).

Six of these studies controlled for antidepressant effects (Boggio et al., 2010; Mantovani et al., 2010; Prasko et al., 2006; Rossini et al., 2010; Sachdev et al., 2007; Sarkhel et al., 2010). This is important, since application of rTMS to the PFC has antidepressant effects (Herrmann and Ebmeier, 2006; Shah et al., 2008) and since comorbid depression is common in patients with OCD (Abramowitz et al., 2007). 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 (George et al., 2009, 1996).

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 OCD (George et al., 2009, 1996).

5.2. Post-traumatic stress 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 (Pallanti and Bernardi, 2009). Neuroimaging studies have demonstrated that PTSD is associated with hyperactivity of the amygdala and hypoactivity in the PFC (Bremner, 2002, 2004, 2005, 2006; Shin et al., 2006). Several studies had indicated abnormalities involving the PFC, in particular the OFC and the DLPFC, and limbic regions, particularly the right hemisphere (Cohen et al., 2004; Ferrari et al., 2008). Accordingly, rTMS applied to the PFC has been considered as a potential therapeutic technique for PTSD treatment (Pigot et al., 2008). Consequently, 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 (Pallanti and Bernardi, 2009; Zwanzger et al., 2009). Accordingly, 2 non-controlled studies (Grisaru et al., 1998; Rosenberg et al., 2002) and 2 controlled were conducted (Cohen et al., 2004; Prasko et al., 2007).

Grisaru et al. 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 (Grisaru et al., 1998). rTMS application led to a significant reduction in PTSD symptoms (i.e., avoidance, anxiety and somatization) as reflected in both the SCL-90 and CGI-S. These effects lasted for 24 h to 28 days.

Rosenberg et al., 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 1 Hz-rTMS and 6 for 5 Hz-rTMS) administered at 90% MT for 15 min (600 pulses/day) over the left PFC (Rosenberg et al., 2002). 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 as rated on the Profile of Mood States (POMS).

Cohen et al. administered 10 sessions (5 days per week for 2 weeks) of rTMS to 24 PSTD patients, with 1 Hz-rTMS ($n = 8$), 10 Hz-rTMS ($n = 10$) or sham-rTMS ($n = 6$) administered at 80% MT for 20 min over the right DLPFC (Cohen et al., 2004). The group that was treated with 1 Hz-rTMS received 100 stimuli per day, in contrast to 10 Hz-rTMS and a sham-rTMS group that received 400 stimuli per day. When compared to the other groups, the 10 Hz-rTMS group showed improvements of PTSD symptoms (re-experiencing and avoidance) in the PTSD Checklist and Treatment Outcome for PTSD scale. Also, a significant reduction of general anxiety levels, lasing for 14 days, was observed.

Boggio et al. 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 ($n = 10$) (Boggio et al., 2010). The authors showed that 20 Hz-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, 20 Hz-rTMS applied to the right DLPFC had a larger effect as compared to the left DLPFC, remaining long-lasting and significant at the 3-month follow-up. Moreover, a significant improvement of mood after application of 20 Hz-rTMS to the left DLPFC and a significant reduction of anxiety following application to the right DLPFC were reported.

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 (Boggio et al., 2010; Cohen et al., 2004). 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 (Thomson and Craighead, 2008). 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 (George et al., 2009, 1996).

With regard to the findings of the rTMS application over the left hemisphere areas, the antidepressant effects of rTMS are already expected due to comorbidity with depression often observed in patients with anxiety disorders. On the other hand, the findings regarding the effects of high-rTMS application over these areas do not support the hypothesis that the activity of fronto-subcortical circuits can arguably be diminished by increasing the activity in the indirect pathway by stimulating areas of left hemisphere, mainly DLPFC, by high-rTMS (George et al., 1996; Pallanti and Bernardi, 2009).

5.3. Panic disorder (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 (Mayberg et al., 1999; Nordahl et al., 1998; Prasko et al., 2004; van den Heuvel et al., 2005).

After extensive search for reliable evidence (George et al., 2009; Pallanti and Bernardi, 2009; Pigot et al., 2008; Zwanzger et al., 2009), only one controlled study was found: Prasko et al. 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 (Prasko et al., 2006). 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 active-rTMS and sham-rTMS groups.

5.4. Generalized anxiety disorder (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 (Pallanti and Bernardi, 2009). 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 (Krain et al., 2008). For instance, in a fMRI study, Monk et al. demonstrated a strong and negative coupling between right amygdala and right ventrolateral prefrontal cortex (vlPFC) when subjects were asked to respond to angry faces (Monk et al., 2008). 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 (Damsa et al., 2009; Pallanti and Bernardi, 2009).

In line with the model for human anxiety proposed for Ressler and Mayberg (2007), the application of 1 Hz-rTMS over PFC has demonstrated benefits in PTSD patients (Boggio et al., 2010; Cohen et al., 2004). 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. intended to identify in GAD patients a critical area of activation within the PFC that could be used to target rTMS treatment (Bystritsky et al., 2009). 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. The authors showed 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 (George et al., 2009), 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 (Gorman, 1996).

6. Conclusions

Up to date, 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 (Prasko et al., 2006, 2007; Sachdev et al., 2007), indicating that any positive clinical effect may be largely attributed to a placebo effect. Many of these questions must be answered before a proper clinical trial can be designed.

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 sub-cortical areas, such as amygdala, hippocampus and striatum, which are most likely to be relevant to the pathogenesis of anxiety disorders (Ressler and Mayberg, 2007). Effects in sub-cortical areas are thought to be indirect, via trans-synaptic connections (George et al., 1996). 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, we must remember that however exciting the neurobiological mechanisms might be, the clinical usefulness of rTMS will be determined by their 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.

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