INSTITUTO DE PSIQUIATRIA-IPUB
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FLÁVIA DE ABREU AUGUSTO PAES

ESTIMULAÇÃO MAGNÉTICA TRANSCRANIANA REPETITIVA (EMTr) APLICADA COMO TERAPIA ADICIONAL AO TRATAMENTO DE ANSIEDADE SOCIAL: UMA REVISÃO DA LITERATURA E TRÊS CASOS CLÍNICOS

RIO DE JANEIRO
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Tese de Doutorado

Orientador: ANTONIO EGIDIO NARDI
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Tese de Doutorado submetida ao Corpo Docente do Programa de Pós-Graduação em Psiquiatria e Saúde Mental - PROPSAM do Instituto de Psiquiatria da Universidade Federal do Rio de Janeiro, como parte dos requisitos necessários para a obtenção do Grau de Doutora em Saúde Mental.

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RIO DE JANEIRO

2015

DEDICATÓRIA

Aos meus pais, Arary Augusto Paes *(in memorian)* e Regina Célia de Abreu Augusto Paes, por me mostrarem a importância do estudo.

Ao meu querido companheiro Sergio Eduardo de Carvalho Machado que teve uma enorme paciência e sempre me apoiou nessa jornada.

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RESUMO

Dentre os transtornos psiquiátricos mais comuns, os transtornos de ansiedade são os mais prevalentes, em torno de 20% na população geral. Esses transtornos são muito incapacitantes e, embora existam métodos de tratamento seguros e eficazes, como farmacoterapia e terapia cognitivo-comportamental (TCC), altas taxas de pacientes refratários ao tratamento são relatadas, aproximadamente 25%. Dessa forma, novos métodos terapêuticos adicionais são necessários. Um possível método que atua modulando a atividade elétrica cerebral e é potencialmente viável para o uso na prática clínica é a estimulação magnética transcraniana repetitiva (EMTr). A EMTr é um procedimento não-invasivo baseado na lei de Faraday de indução eletromagnética, onde um campo magnético ao atingir o tecido cerebral induz uma corrente elétrica, excitando ou inibindo os circuitos neurais, que acredita-se estar desorganizado nos transtornos psiquiátricos. O tratamento com EMTr pode ser considerado um tratamento de neuromodulação cerebral devido ao seu foco ser direcionado aos circuitos neurais de cada transtorno. Embora os resultados positivos tenham sido frequentemente relatados nos estudos não-controlados e nos estudos randomizados, não há nenhuma evidência conclusiva da eficácia da EMTr para o tratamento de transtornos de ansiedade. Até o presente momento, do grupo de transtornos de ansiedade mais investigados, somente o transtorno de ansiedade social (TAS) ainda não foi investigado. Tal fato é de grande relevância já que o TAS tem taxas de prevalência em torno de 12.1% na população geral, ao longo da vida. Portanto, a presente tese teve como objetivo, investigar os efeitos do uso da EMTr de baixa frequência (1 Hz) aplicada no córtex pré-frontal ventromedial direito (CPFVM), em pacientes com TAS refratários à medicação e à TCC. Nesta tese, são apresentados 4 estudos. Os estudos 1 e 2 exploram os conceitos básicos da EMTr, os mecanismos moleculares e celular em modelos animais de transtornos de ansiedade, fatores individuais que interferem na resposta a esta técnica e discutem-se os efeitos da EMTr nos transtornos de ansiedade. O estudo 3 foi o primeiro caso de EMTr em TAS realizado no mundo, onde um paciente com TAS circunscrito, refratário à medicação e à terapia cognitivo comportamental (TCC) recebeu uma única sessão de EMTr de 1Hz a 120% do limiar motor sobre o CPFVM. O paciente apresentou boa redução dos sintomas de depressão, ansiedade e um bom aumento das habilidades sociais. O estudo 4 foi conduzido com outros 2 pacientes com TAS generalizado e depressão comórbida e também refratários à medicação e à TCC, onde os pacientes receberam 12 sessões de EMTr de 1Hz a 120% do limiar motor sobre o CPFVM. No que diz respeito aos dois casos tratados com EMTr, encontramos uma diminuição nos sintomas de depressão, ansiedade e ansiedade social da linha de base ao acompanhamento.

Palavras-chave: Córtex Pré Frontal Ventro Medial, Estimulação Magnética Transcraniana (EMT), Transtorno de Ansiedade Social (TAS), Terapia Cognitivo-Comportamental (TCC).

ABSTRACT

Within the most common psychiatric disorders, anxiety disorders have prevalence around 20%. These disorders can be very disabling and, although there are safe effective methods of treatment, such as pharmacotherapy, and cognitive behavioral therapy (CBT), high rates of refractory patients are reported, approximately 25%. Thus, new additional therapeutic methods are needed. One such method that works by modulating the brain electrical activity and is potentially viable for use in clinical practice is repetitive transcranial magnetic stimulation (rTMS). rTMS is a noninvasive procedure based on Faraday's law of electromagnetic induction, where a magnetic field to reach the brain tissue turns into an electric current, exciting or inhibiting neural circuits, which believed to be disorganized in psychiatric disorders. rTMS can be considered a treatment of brain neuromodulation due to its directed focus on neural circuits of each disorder. Although positive results have been frequently reported in uncontrolled studies and randomized trials, there are no conclusive evidence of the efficacy of rTMS for the treatment of anxiety disorders. To date, from the group most commonly investigated in anxiety disorders, only the social anxiety disorder (SAD) has not been investigated. This fact is very relevant since SAD has prevalence rates around 12,1%, lifelong. Thus, this thesis aimed to investigate the effects of the use of low-frequency rTMS (1 Hz) applied to the right ventromedial prefrontal cortex (VMPFC), in patients with SAD refractory to medication and CBT. In this thesis, we present four studies. The first and second studies explore the basic concepts of rTMS, the molecular mechanisms and the cellular potential in animal models of anxiety disorders, individual factors that interfere with the response to this technique and the effects of rTMS in anxiety disorders. The third study was the first case report of rTMS and SAD carried out in the world where a patient diagnosed with SAD circumscribed, refractory to medication and cognitive behavioral therapy (CBT) received a single session of 1 Hz- rTMS at 120% of motor threshold on the right ventromedial prefrontal cortex VMPFC. The patient presented reduction of depression and anxiety symptoms, and increase in social skills. The forth study was conducted with other 2 patients diagnosed with generalized SAD and comorbid depression and also refractory to medication and CBT, where they received 12 sessions of 1Hz-rTMS at 120% of motor threshold on the right VMPFC. With regard to the two cases treated with rTMS, we found a decrease in BDI, BAI and LSAS scores from baseline to follow-up.

Key-words: Cognitive Behavior Therapy (CBT), ventromedial prefrontal cortex (vmCPF), Social Anxiety Disorder (SAD), Transcranial Magnetic Stimulation (TMS).

LISTA DE SIGLAS

CPFVM = Córtex pré-frontal ventromedial

DSM = Manual Diagnóstico e Estatístico de Transtornos Mentais

EMT = Estimulação magnética transcraniana

EMTr = Estimulação magnética transcraniana repetitiva

TAS = Transtorno de ansiedade social

TCC = Terapia cognitivo-comportamental

SUMÁRIO

INTRODUÇÃO

O transtorno de ansiedade social (TAS) é caracterizado pelo medo, evitação e/ou fuga de situações sociais. Segundo estudos epidemiológicos, o TAS é um dos transtornos psiquiátricos mais comuns, com taxa de prevalência em torno de 12,1% na população geral, ao longo da vida (Kessler et al., 2005a,b). De acordo com a quarta edição do Manual Diagnóstico e Estatístico de Transtornos Mentais (DSM - IV), ele é dividido em 2 subtipos, específico e generalizado. O subtipo específico refere-se ao medo, evitação e/ou fuga de uma situação social específica de desempenho como, por exemplo, falar em público (Freitas-Ferrari et al., 2010). Já o subtipo generalizado envolve o medo, evitação e/ou fuga de situações sociais de forma geral, e por isso os pacientes são, consequentemente, mais comprometidos que os do primeiro subtipo (Kessler et al., 1998).

Em maio de 2013 foi lançada a quinta edição do DSM (DSM-5), trazendo algumas alterações nos critérios diagnósticos dos transtornos mentais. Em relação ao TAS, a mudança mais expressiva foi a substituição dos especificadores generalizado e circunscrito para apenas o especificador “desempenho”. Vale lembrar que a presente tese foi realizada com os critérios diagnósticos do DSM IV-TR, lançado em 2000. Portanto, como os dados foram coletados antes do lançamento do DSM-5, os resultados não foram comprometidos com conflitos nas interpretações.

Apesar da alta prevalência do TAS na população geral e do significativo comprometimento social e ocupacional relacionados a ele (Schneier, 2003; Stein, 2006), pouca atenção foi dedicada ao estudo de seus mecanismos neurobiológicos nos últimos anos (Bell et al., 1999), quando um aumento considerável no número de estudos com intuito de elucidar os aspectos fisiopatológicos da doença foi observado (Crippa, 2009, Stein e Stein, 2008).

Com relação aos circuitos neurais envolvidos no TAS, ainda não há um consenso sobre quais áreas realmente os compõem. Nesse sentido, estudos clínicos e pesquisas envolvendo modelos animais (Gelernter et al., 2004), além de estudos utilizando técnicas de neuroimagem, como por exemplo, ressonância magnética funcional (RMf) e tomografia por emissão de pósitrons (TEP), têm procurado ajudar a encontrar a melhor maneira de compreender esses circuitos neurais (Ferrari et al., 2008). Sendo assim, Freitas-Ferrari et al. (2010), verificaram em uma recente revisão de estudos de neuroimagem, que as regiões pré-frontais, mais especificamente o córtex pré-frontal ventromedial direito (CPFVM), estão hiperativadas e os córtices parietal e estriado estão hipoativados mediante de exposição a expressões faciais de emoção, paradigmas de provocação de sintomas, e anormalidades relacionadas com a neurotransmissão de dopamina ou serotonina.

Muito embora existam tratamentos eficazes e seguros, como medicamentos e psicoterapia, muitos pacientes com TAS não respondem a este modelo tradicional de tratamento (Ganasen e Stein, 2010). No entanto, com os avanços nos últimos anos em relação aos mecanismos neurobiológicos envolvidos no TAS, novos tratamentos têm sido propostos, tal como a estimulação magnética transcraniana (EMT). A EMT é um método não-invasivo, seguro e indolor (Barker, 1985; Hallett, 2007; Rossi et al., 2009; Paes et al., 2011), baseada na lei de Faraday de indução eletromagnética, segundo a qual uma corrente elétrica é induzida no tecido cortical por um campo magnético gerado por uma bobina elétrica colocada sobre o escalpo, com o objetivo de despolarizar ou hiperpolarizar os neurônios. No seu formato repetitivo, a EMTr pode modular a excitabilidade cortical, no entanto, isso dependerá da localização (área alvo), intensidade (limiar motor) e frequência (lenta e rápida) dos pulsos magnéticos utilizados (Hallett, 2007; Paes et al., 2011).

A intensidade é determinada pelo limiar motor (LM) (Hallett, 2007). O LM é uma medida da excitabilidade de membrana neuronal do trato córtico-espinal (Paes et al., 2011;

Machado et al., 2012). O LM em repouso corresponde à menor intensidade de estímulo capaz de evocar potenciais motores evocados (PEMs) de no mínimo 50 mV de amplitude, em pelo menos 5 de 10 pulsos magnéticos administrados, sobre o músculo-alvo em repouso (Paes et al., 2011). Portanto, o LM é utilizado como referência para definir a intensidade e as outras variáveis para uso terapêutico da EMT (Machado et al., 2012). Já as frequências podem ser baixa e alta. A baixa frequência se dá quando os pulsos ocorrem numa frequência até 1Hz, e alta frequência se dá quando os pulsos ocorrem numa frequência superior a 1Hz (Hallett, 2007). Esta classificação baseia-se nas diferenças fisiológicas encontradas entre os dois tipos de estimulação, onde altas frequências promovem um efeito, em geral, excitatório, e a de baixa frequência gera um efeito inibitório (Paes et al., 2013).

Desde sua introdução, EMTr apresentou um potencial terapêutico em algumas doenças neuropsiquiátricas, como depressão e esquizofrenia contudo, em transtornos de ansiedade, mais especificamente no TAS, somente nosso estudo foi realizado com o intuito de investigá-lo. A EMTr pode ser considerada um tratamento de neuromodulação porque tem o objetivo de ajustar os circuitos neurais que acredita-se estarem desorganizados nos transtornos psiquiátricos (Paes et al., 2011).

Nesta tese de doutorado, são abordados pacientes com diagnóstico de Transtorno de Ansiedade Social (TAS). Esta psicopatologia possui características bem particulares com relação ao funcionamento cerebral e comportamental. Dessa forma, como todo trabalho inédito, foi necessário supor certas hipóteses. Portanto, baseando-se na hipótese de valência (Heller, 1997; Prete et al., 2015), que propõe que o padrão de dominância hemisférica depende da valência emocional do estímulo, ou seja, o hemisfério esquerdo é dominante para processamento de emoções positivas, enquanto que o hemisfério direito é dominante para o processamento de emoções negativas. Conforme a hipótese de valência, medo, raiva, desgosto e tristeza, por exemplo, são emoções negativas consideradas, e felicidade e surpresa são

classificados como emoções positivas. E em achados de neuroimagem (Freitas-Ferrari, 2010) citados anteriormente, que também deram suporte para a construção de um racional fisiopatológico. Levando tudo isso em consideração, o foco de estimulação para o TAS seria a área pré-frontal ventro-medial direita, correspondente a posição do eletrodo FP2 do sistema internacional 10/20 de EEG, já que está área mostra-se hiperativada no TAS e é dominante para o processamento de emoções negativas como já foi observado em diversos estudos com provocação de estímulos e exposição a faces com expressões emocionais (Freitas-Ferrari et al., 2010).

O primeiro artigo publicado sobre o tema foi uma revisão na CNS & Neurological Disorders em 2011 (Paes et al., 2011). Nesse artigo abordou-se a importância de estudar a EMTr aplicada aos diversos transtornos de ansiedade pela alta frequência que essa psicopatologia apresenta na literatura, elencando uma série de estudos que utilizam a EMTr como ferramenta nos transtornos de ansiedade. Foram explorados os conceitos fisiológicos e físicos da estimulação são explorados e são discutidos os resultados encontrados em modelos animais.

O segundo artigo (Machado et al., 2012) é iniciado mostrando a importância de ferramentas alternativas para tratar pacientes com transtornos de ansiedade refratários aos tratamentos tradicionais. São discutidos os fundamentos básicos da estimulação magnética transcraniana e fatores individuais que interferem na resposta a esta técnica, e também os mecanismos moleculares e o potencial celular em modelos animais de transtornos de ansiedade, e finalizando com os efeitos da EMTr em paciente com transtornos de ansiedade.

O primeiro artigo no mundo realizado sobre o tratamento com EMTr para TAS foi escrito pelo nosso grupo de pesquisas do Laboratório de Pânico e Respiração (LABPR) e publicado na Revista Brasileira de Psiquiatria em 2013 (Paes et al., 2013a). O estudo de caso abordou um paciente de 38 anos com TAS circunscrito, refratário à medicação e à terapia

cognitivo comportamental (TCC). Neste estudo, como foi um caso inicial, foi realizada uma única sessão de 1Hz à 120% do LM por 25 minutos (1500 pulsos) sobre o CPFVM direito.

Outros dois casos clínicos foram publicados no mesmo ano que o estudo anterior, na revista Clinical Pratice & Epidemology in Mental Health (Paes et al., 2013b). Foram dois pacientes ambos diagnosticados pelos critérios do DSM IV-TR com TAS generalizado e depressão comórbidos e também refratários à medicação e à TCC. Neste estudo, foi realizado um protocolo de tratamento de 1Hz à 120% do LM por 25 minutos (1500 pulsos) sobre o CPFVM direito, de 3 vezes por semana durante 4 semanas.

Portanto, a presente tese teve como objetivos, (1) estudar os conceitos físicos e fisiológicos da EMT, (2) apresentar a importância dos efeitos de sham-EMTr e parâmetros de estimulação, (3) revisar os principais achados da EMTr em modelos animais, (4) discutir as principais informações e conclusões relacionadas com o potencial terapêutico da EMTr nos transtornos de ansiedade, e (5) verificar os efeitos da EMTr no TAS nos estudos de caso estudados e discutir possíveis avanços experimentais que podem tornar viável a EMTr como aplicação clínica nos próximos anos.

ARTIGO 1

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

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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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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

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

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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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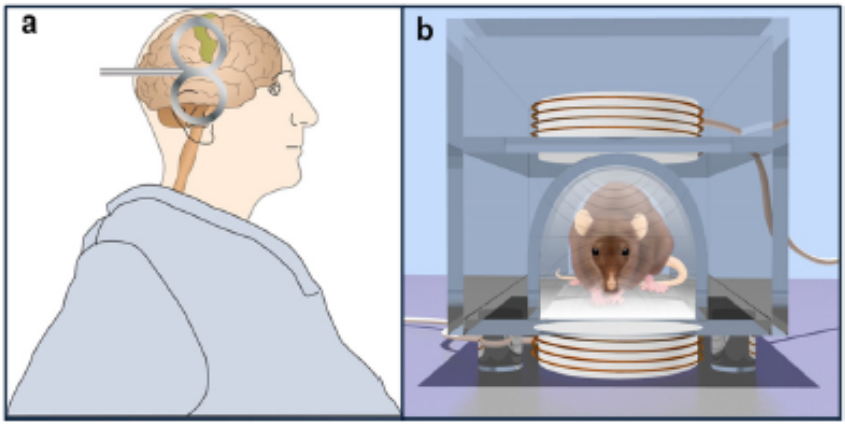

Fig. 1. Repetitive transcranial magnetic stimulation (rTMS) in humans and rodents. According to the evidence cited in this review, there are basically two types of coils: round coils which are relatively non focal and figure-of-eight-shaped coils used to stimulate specific areas, producing maximal current 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 ORC 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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ARTIGO 3

rTMS to treat social anxiety disorder: a case report

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Letter to the Editors

rTMS to treat social anxiety disorder: a case report

Dear Editor,

Social anxiety disorder (SAD) is one of the most common and debilitating types of anxiety disorders. Nevertheless, little attention has been dedicated to the study of the neurobiology underlying SAD until the last decade.[1] Approximately 25% of anxiety disorder patients, including SAD patients, are non-responders to traditional methods of treatment.[2] Thus, advances in our understanding of the neural basis involved in SAD could lead to new therapeutic options.[1] One such novel therapeutic option is repetitive transcranial magnetic stimulation (rTMS), a non-invasive procedure whereby a pulsed magnetic field stimulates electrical activity in the brain and depolarizes neurons.[2] We report a case of a 38 year old single male. The patient signed a consent form and was aware of the experimental protocol (approved by the Ethics Committee at Universidade Federal do Rio de Janeiro) before participation commenced.

The patient was diagnosed with specific SAD (writing in public), without comorbidities according to DSM-IV-TR. The patient was treatment-resistant to a serotonin-specific reuptake inhibitor (SSRI) and cognitive behavior therapy (CBT). A single session of rTMS was administered at 1Hz (inhibitory frequency) at 120% MT for 25 min (1,500 pulses) over the right ventromedial prefrontal cortex (vmPFC). The vmPFC represents the most promising target for rTMS because this structure is consistently activated in SAD.[1] The right vmPFC is located near the Fp2 position according to an EEG-international 10/20 electrode scalp positioning system. Through this system, satisfactory activation of cortical areas may be reached reliably on a larger scale.[3]

Assessments were carried out pre- and post-treatment using the Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI) and Social Skills Inventory (SSI). Pre-treatment results were the following: BDI 18 (moderate), BAI 21 (moderate). Post-treatment results were the following: BDI 19 (moderate), BAI 5 (minimal). At a 2-month follow-up, we obtained the following results: BDI 13 (minimal) and BAI 13 (mild) (Figure 1A). With respect to SSI, there were changes in social skill performance in 12 (8 positives and 4 negatives) of 32 issues between the pre-treatment and the post-treatment periods and in 16 (10 positives and 6 negatives) of 32 issues between the post-treatment and the follow-up periods (Figure 1B).

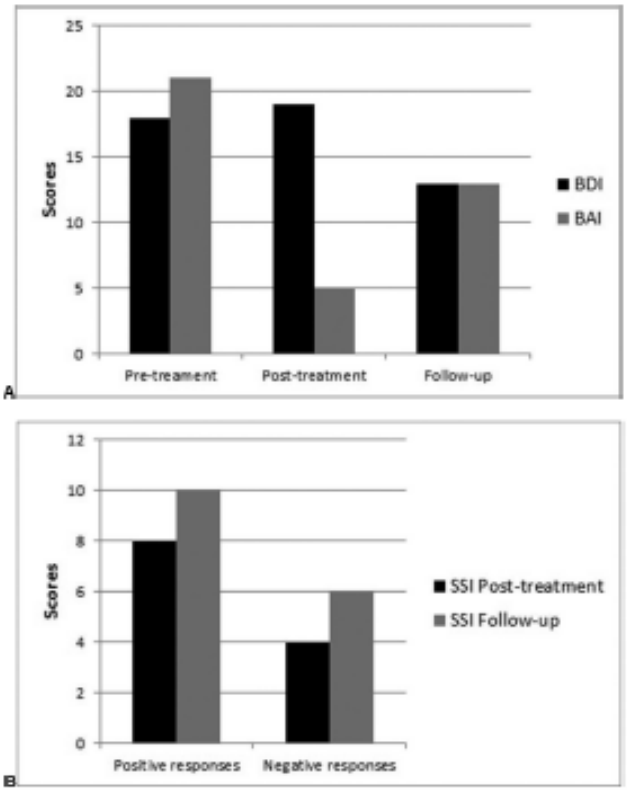

Figure 1 Scores of Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI) and Social Skills Inventory (SSI) related to rTMS application. (A) Scores of BDI and BAI at pre- and post-treatment and at follow-up. (B) Scores of positive and negative responses to SSI at post-treatment and follow-up.

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Discussion

Prior to the rTMS session, the patient presented a moderate level of anxiety, reporting for example, an inability to relax, nervousness, and a fear of the worst happening (areas most highly rated on BAI). One week after the rTMS session, the patient showed large reduction in anxiety symptoms compared to pre-treatment. With regard to social skills performance, the patient showed a mild reduction post-treatment compared to pre-treatment. The patient reported a greater likelihood to join conversations, to have a sense of humor, and to offer help to peers (areas most highly rated on SSI). These findings suggest that 1Hz rTMS over the vmPFC (a brain area responsible for emotional regulation)[4] promoted the reinterpretation and reprocessing of events regarding the patient's anxiety level and social skills performance in a more controlled and therapeutic manner. During the two-month follow-up, the patient still presented low-level anxiety and similar social skills performance compared to pre-treatment with a slight increase compared to post-treatment. However, without a placebo control, these assumptions are merely speculative at this point.

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* *Modest*
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*** *Significant. Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author.*

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ARTIGO 4

Repetitive Transcranial Magnetic Stimulation (rTMS) to Treat Social Anxiety Disorder: Case Reports and a Review of the Literature

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Repetitive Transcranial Magnetic Stimulation (rTMS) to Treat Social Anxiety Disorder: Case Reports and a Review of the Literature

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Abstract: *Objectives:* Social anxiety disorder (SAD) is a common and debilitating anxiety disorders. However, few studies had been dedicated to the neurobiology underlying SAD until the last decade. Rates of non-responders to standard methods of treatment remain unsatisfactorily high of approximately 25%, including SAD. Advances in our understanding of SAD could lead to new treatment strategies. A potential non invasive therapeutic option is repetitive transcranial magnetic stimulation (rTMS). Thus, we reported two cases of SAD treated with rTMS *Methods:* The bibliographical search used *Pubmed/Medline, ISI Web of Knowledge* and *Scielo* databases. The terms chosen for the search were: anxiety disorders, neuroimaging, repetitive transcranial magnetic stimulation. *Results:* In most of the studies conducted on anxiety disorders, except SAD, the right prefrontal cortex (PFC), more specifically dorsolateral PFC was stimulated, with marked results when applying high-rTMS compared with studies stimulating the opposite side. However, according to the "valence hypothesis", anxiety disorders might be characterized by an interhemispheric imbalance associated with increased right-hemispheric activity. With regard to the two cases treated with rTMS, we found a decrease in BDI, BAI and LSAS scores from baseline to follow-up. *Conclusion:* We hypothesize that the application of low-rTMS over the right medial PFC (mPFC; the main structure involved in SAD circuitry) combined with high-rTMS over the left mPFC, for at least 4 weeks on consecutive weekdays, may induce a balance in brain activity, opening an attractive therapeutic option for the treatment of SAD.

Keywords: Dorsolateral prefrontal cortex, medial prefrontal cortex, repetitive transcranial magnetic stimulation, social anxiety disorders, valence hypothesis.

INTRODUCTION

Social anxiety disorder (SAD) is one of the most common anxiety disorders, characterized by fear and avoidance of social situations [1]. SAD can be divided into two subtypes: specific and generalized SAD. Specific SAD refers to the fear and avoidance of a particular performance situation such as public speaking, while generalized SAD refers to fear and avoidance of a wide array of social situations, with subsequently stronger impairing effects as compared to specific SAD [1]. SAD is very debilitating and despite its high prevalence [2, 3], little attention had been dedicated to the study of the neurobiology underlying SAD until the last decade [4]. However, with the considerable increase in the number of studies in the last years, aiming to elucidate the physiopathological aspects of SAD [5,6], together with clini-

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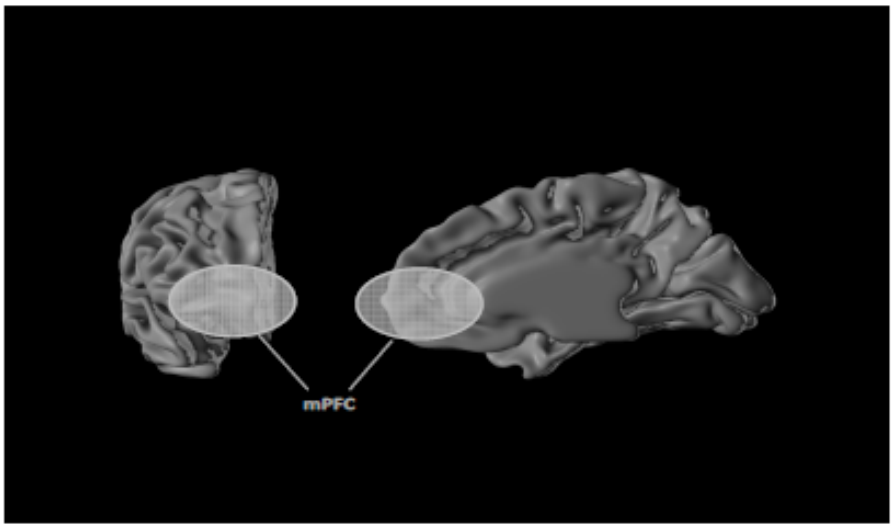

Fig. (1). The medial prefrontal cortex (mPFC). The left image shows the frontal pole of the right brain hemisphere, the yellow mark is the external view of the right mPFC while the right image shows an internal projection of the right mPFC, the main brain structure related to social anxiety disorder.

cal reports, animal models, genetic [7], and neuroimaging studies, a better comprehension of the neural circuitry underlying SAD has been achieved [8].

Anxiety disorders have a lifetime prevalence of greater than 20%, and although there are several methods of treatment available (i.e., pharmacotherapy and cognitive-behavioral therapy), high rates of non-responders to these treatments are reported, namely, approximately 25%, including SAD [9, 10]. Thus, searching for new alternative treatments is essential. Advances in our understanding of the neurobiological mechanisms involved in SAD could lead to new therapeutic options. One such novel therapeutical option is repetitive transcranial magnetic stimulation (rTMS), a non-invasive procedure whereby a pulsed magnetic field stimulates electrical activity in the brain and depolarizes neurons [11]. rTMS can be considered a brain-system-based neuromodulation treatment due to its ability of directly targeting the neural circuitry of several psychiatric and/or neurological disorders [12]. 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 case of certain disorders [9,10,12].

However, until today, there is no consensus about the brain circuitries underlying SAD. Several studies have reported the participation of amygdala, medial frontal cortex, insular cortex, and cingulate cortex [13,14]. However, a recent systematic review [1] stated that medial prefrontal cortex (mPFC) is the structure most consistently activated in all studies on SAD (Fig. 1). Hence, the mPFC represents a promising candidate region for being targeted with a non-invasive brain stimulation technique such as rTMS.

This review aims to provide information on the current research and main findings related to brain circuitries involved in SAD, rTMS protocols used for treating anxiety disorders, the rationale of rTMS on Social Phobia treatment and two cases of SAD treated with rTMS. Thus, we hypothesize that the optimal rTMS regime for treating SAD, based on the "valence hypothesis", is to use low-rTMS over the right mPFC.

METHODS

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, metaanalyses 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 in Social Phobia.

BRAIN CIRCUITRIES INVOLVED IN SOCIAL ANXIETY DISORDER

Neuroimaging techniques allow for an *in vivo* assessment of the functional architecture of the human brain, leading to a better understanding of its anatomical and functional state [15]. Up to the last decade, little attention had been dedicated to neurobiological mechanisms underlying SAD, however, it has been demonstrated that the identification and location of abnormal brain functioning depend on the type of anxiety disorder [8].

Several neuroimaging studies have demonstrated that amygdala and mPFC play a key role in the attribution of emotion-related stimuli in SAD [16-19]. Generally, these findings suggest a deficit in top-down modulation of execu-

tive processes, such as associative, attentional and interpretative control [20]. In theory, the abnormal functioning of circuitries in SAD would result in impaired top-down modulation, i.e., impairment in the connectivity and cross-talk between amygdala and prefrontal brain areas. Prefrontal areas, which are also responsible for inhibitory responses, could lead to increased responsiveness of the amygdale [21].

Based on results from animal studies, Bishop [22] proposed that a down regulation of amygdala output may be brought about by two distinct process: i) through an excitation of gamma-aminobutyric acid (GABA) pathways within the basolateral complex of the amygdala, or ii) through an excitation of the nearby intercalated cells via mPFC neurons. In line with this view, clinical and neuroimaging results have demonstrated that selective attention is associated with emotion-related stimuli involved in dysfunctional prefrontal inhibition, and with amygdala hyperactivity during the processing of potentially threatening information from the environment [23, 24].

There is also evidence of decreased activity in prefrontal areas during anxiety provocation in patients with SAD, probably reflecting impaired cognitive processing [25-28], and increased activity in prefrontal areas during provoked anticipatory anxiety [29, 30]. There are two rationales for these apparent discrepancies: i) functional responses of the mPFC are dependent on the nature of the cognitive-emotional task employed [31] and ii) the mPFC is subdivided into distinct neuroanatomical and functional areas [32]. In a similar vein, several studies have concretely proposed that the mPFC can be functionally divided into two different parts: i) a ventral region, mainly related to self-referential/relevant processing [33, 34] and ii) a dorsal region, related to theory of mind, such as contemplating about other people's mental states [35, 36]. The study of Blair *et al.* [37] used functional magnetic resonance imaging (fMRI) to reveal that SAD patients had significant responses to self-referential criticism in more dorsal regions of the cortex. These findings regarding mPFC subregions could be used as a guide for new investigations in SAD, using neuroimaging methods and specific cognitive tests. Amir *et al.* [38], e.g., demonstrated an association between anterior cingulated cortex (ACC) (i.e., a part of the mPFC) and the negative emotion in SAD patients viewing disgusted facial expressions. The dorsal ACC is thought to recruit the dorsolateral mPFC in order to select and implement regulatory strategies, directing attention control, and reducing cognitive conflicts [39]. Therefore, impairment of early recruitment of dorsal ACC and dorsolateral mPFC during cognitive reassessment could trigger emotion regulation problems in SAD patients [40].

RTMS PROTOCOLS USED FOR TREATING ANXIETY DISORDERS

A few studies have been conducted in order to investigate the therapeutic effects of rTMS on anxiety disorders, but not on SAD (see Table 1). Even though positive effects have been found in both, controlled and non-controlled studies, there are still no established protocols for rTMS treatment in anxiety disorders. Perhaps the lack of standard rTMS treatment may be due to the varying treatment parameters used in these studies, making the interpretation of the results difficult [10].

The first evidence of a putative anxiolytic action of rTMS in humans was based on the so called ''valence-hypothesis'' [41], which has been proposed for human anxiety. According to this model, patients with anxiety disorders are characterized by an interhemispheric imbalance that might be associated with increased right-hemispheric activity [9, 10].

First empirical support for this model was reported by two studies applying 1 Hz-rTMS over the right prefrontal cortex (PFC) [42, 43]. They demonstrated anxiolytic effects of slow-frequency rTMS over the right mPFC after inducing anxiogenic states in healthy individuals. In contrast, other studies examined the hypothesis that not low- but high-frequency-rTMS over the left dorsolateral prefrontal cortex (DLPFC) is effective in the treatment of anxiety disorders [44, 45], a rationale that is supported by the cerebral hyperexcitability and the behavioral and cognitive activation that is commonly observed in neuropsychiatric disorders [46]. The activity of fronto-subcortical circuits can arguably be diminished by increasing the activity in the indirect pathway by stimulating the left DLPFC with high-rTMS [44, 45].

Several controlled and non-controlled TMS studies in anxiety disorders have recently been reported, with the use of either low- and/or high-frequency rTMS applied to either left and/or right hemisphere, especially in PFC areas, such as the DLPFC and orbitofrontal cortex (OFC). Intriguingly, despite the fundamental differences in rTMS frequencies that were used and/or hemispheric lateralization that was targeted, all of these studies demonstrate promising positive effects with regard to a TMS-induced reduction of anxiety symptoms. Concretely, six studies explored active-rTMS over the right hemisphere, with two stimulating with high-frequency rTMS [47, 48] and four with low-frequency rTMS [49-52]. Three studies explored active-rTMS over the left hemisphere, with one stimulating with high-frequency rTMS [53] and two with low-frequency rTMS [54, 55]. In addition, one study compared the low- and high-frequencies in the right hemisphere [56] and another study did so for the left hemisphere [57]. Again two studies applied high-frequency rTMS over both hemispheres [58, 59]. However, only few studies demonstrated statistically significant differences between active and sham treatment [47, 55, 56].

Hence, although positive results have frequently been reported in both non-controlled and controlled studies, there is no conclusive evidence of the efficacy of rTMS for the treatment of anxiety disorders. Several, sometimes contradictory, treatment parameters have been used in the different studies, making the interpretation of the results difficult. Most studies, therefore, do not support the notion that active-rTMS, as hitherto applied, is an effective treatment for obsessive-compulsive disorder (OCD) and posttraumatic stress disorder (PTSD). In the literature on the therapeutic effects of rTMS 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, only three TMS studies on anxiety disorders have assessed the effects of rTMS compared to sham-rTMS over at least 4 weeks [49, 55, 60]. Moreover, in

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 20Hz of 80% MT PFC–L 20Hz of 80% MT Occipital 20Hz 80% MT	Reduction in OCD symptoms only with right-sided treatment.*
Sachdev *et al.* 2001	Open study 10 sessions (5 days per week for 2 weeks)	12	PFC–R 10Hz of 110%MT PFC–L 10Hz of 110% MT	Both groups showed a significant reduction in OCD symptoms.* However, no significant difference was noted between groups.
Alonso *et al.* 2001	RCT 18 sessions (3 days per week for 6 weeks)	18	DLPFC–R 1Hz of 110% MT Sham-rTMS	Slight reduction in OCD symptoms in rTMS group.* However, no significant difference was noted between groups.
Mantovani *et al.* 2006	Open study 10 sessions (5 days per week for 2 weeks)	10	SMA–bilaterally 1Hz of 100% MT	Significant reduction in OCD symptoms.*
Prasko *et al.* 2006	RCT 10 sessions (5 days per week for 2 weeks)	30	DLPFC–L 1Hz of 110% MT Sham-rTMS	Both groups showed a significant reduction in anxiety.* However, no significant difference was found between groups.
Sachdev *et al.* 2007	RCT 10 sessions (5 days per week for 2 weeks)	18	DLPFC–L 10Hz of 110% MT Sham-rTMS	No significant difference was found between groups. However, after comparison, all subjects received rTMS showed a significant reduction in OCD symptoms.
Kang *et al.* 2009	RCT 10 sessions (5 days per week for 2 weeks)	20	DLPFC–R 1 Hz of 110% MT SMA–bilaterally 1Hz of 100% MT Sham-rTMS	No significant difference was found on both groups and between groups.
Ruffini *et al.* 2009	RCT 15 sessions (5 days per week for 3 weeks)	23	OFC–L 1Hz of 80% MT Sham-rTMS	Significant reduction in OCD symptoms in favor of rTMS compared to sham-rTMS.* However, no significant reduction in anxiety and depression symptoms was found between groups.
Mantovani *et al.* 2010	RCT 20 sessions (5 days per week for 4 weeks)	18	SMA–bilaterally 1Hz of 100% MT Sham-rTMS	Significant reduction in OCD symptoms in favor of rTMS compared to sham-rTMS.*
Sarkhel *et al.* 2010	RCT 10 sessions (5 days per week for 2 weeks)	42	PFC–R 10Hz of 110% MT Sham-rTMS	Significant reduction in OCD symptoms and a significant improvement in mood in both groups.* However, no significant difference was observed between groups.
PTSD				
Grisaru et al. 1998	Open study 1 session	10	Motor cortex–R of 0.3 Hz of 100% MT Motor cortex–L of 0.3 Hz of 100% MT	Significant reduction in anxiety, and PTSD symptoms.*
Rosenberg et al. 2002	Open study 10 sessions (5 days per week for 2 weeks)	12	DLPFC–L 1Hz of 90% MT DLPFC–L 5 Hz of 90% MT	Significant improvement of insomnia, hostility and anxiety, but minimal improvements in PTSD symptoms.* However, no significant different was noted between groups.

Table 1. contd...

Study OCD	Design	N	rTMS Protocol	Efficacy
Cohen et al. 2004	RCT 10 sessions (5 days per week for 2 weeks)	24	DLPFC–R 1Hz of 80%MT DLPFC–R 10Hz of 80%MT Sham-rTMS	Significant improvement of PTSD symptoms and a significant reduction in general anxiety levels in favor of 10Hz-rTMS group when compared to other groups.*
Boggio *et al.* 2010	RCT 10 sessions (5 days per week for 2 weeks)	30	DLPFC–L 20Hz of 80%MT DLPFC–R 20Hz of 80%MT Sham-rTMS	Significant reduction in PTSD symptoms, anxiety and improvement of mood in favor of rTMS compared to sham-rTMS.*
PD				
Prasko *et al.* 2007	RCT 10 sessions (5 days per week for 2 weeks)	15	DLPFC–R 1Hz of 110% MT Sham-rTMS	Both groups showed a significant reduction in anxiety symptoms.* However, no significant difference was found between groups for PD symptoms.
GAD				
Bystrisky *et al.* 2008	Open study 6 sessions (2 days per week for 3 weeks)	10	DLPFC–R 1Hz of 90% MT	Significant reduction in anxiety symptoms.*

*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.

one of these studies, rTMS was only given five-times per week by Ruffini *et al.* [55]. Two other studies may have been underpowered, suggesting that results could be attributed to a type II error [49, 54], and probably due to the low placebo response reported in patients. In line with this notion, Sachdev and colleagues [53] inferred that, given the effect size in their study, a very large sample would have been required to demonstrate a significant group difference.

Sham-controlled research has often been unable to distinguish between response to rTMS and sham treatment. Within this context, all sham-controlled studies used methods that are recognized to provide adequate blinding (i.e., active coil, 45° or 90° to the head or inactive coil on the head with active coil discharged in 1 m-distance) [47-49, 51, 52, 54-56, 59]. However, only 4 studies showed significant differences between rTMS and sham treatment [47, 55, 56, 60].

Moreover, only four studies controlled for antidepressant effects [47, 48, 54, 55]. This is important, since application of rTMS to the PFC can have antidepressant effects [61,62] and since comorbid depression is common in patients with anxiety disorders [63]. As such, it is very difficult to assess the effects of rTMS on anxiety disorders independent of depression.

Finally, there is a limitation in the rTMS technique itself which impacts only the superficial cortical layers directly. It is possible to also affect 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 [9, 10, 44, 64].

With regard to theoretical conceptualizations, the reported effects of rTMS over right PFC for reducing anxiety symptoms are possibly brought about by re-establishing the connectivity between an underactive PFC, which is theorized to mediate amygdala activity and amygdala hyperactivity, by increasing PFC activity, suggesting that high-rTMS might be an optimal treatment strategy. Alternatively, these results could be associated with increased activation of the hypothalamic-pituitary-adrenal (HPA) axis, suggesting an association between right prefrontal and HPA axis hypoactivity. 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 [65].

The findings of antidepressant effects of rTMS application over the left hemisphere with are to be expected due to comorbidity with depression often observed in patients with anxiety disorders. However, the findings regarding the effects of rTMS application over these areas do not support the hypothesis that the activity of fronto-subcortical circuits can be diminished by increasing the activity in the indirect pathway by stimulating areas of the left hemisphere, mainly the DLPFC, by high-rTMS [44, 45].

RTMS AND SOCIAL PHOBIA: WHAT IS THE RATIONALE?

While the main focus of the possible therapeutic effects of TMS has been mainly in the domain of depression, there are now a significant number of studies that have explored the possibility of using rTMS for treating anxiety disorders. In most of these studies, both, non-controlled and controlled, in which the right PFC, more specifically the DLPFC was stimulated, conflicting results were found in comparison with the studies that investigated the effects of rTMS in the

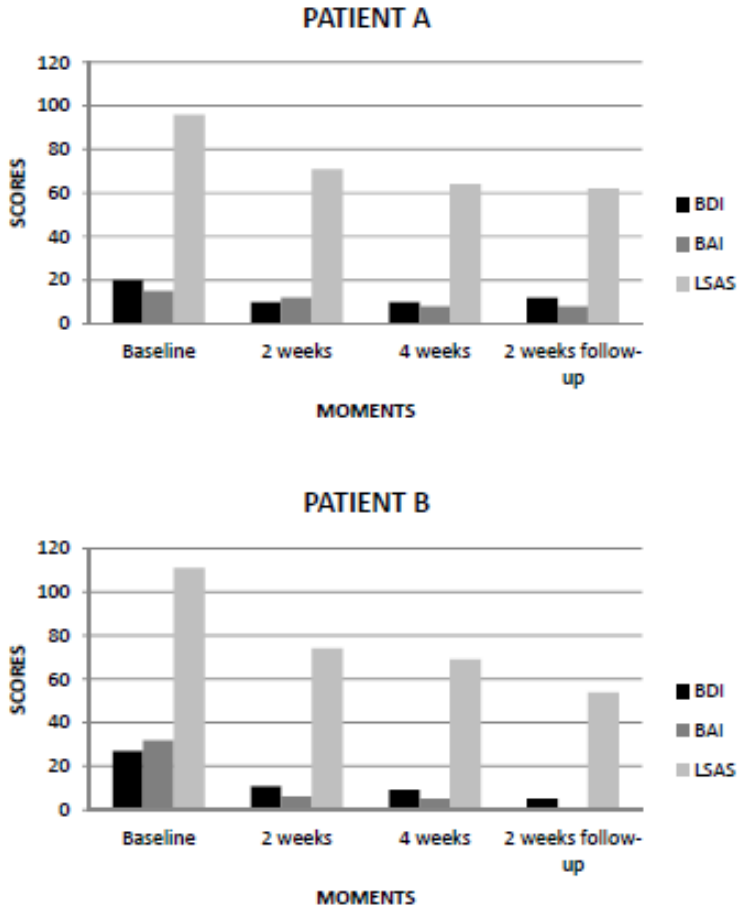

Fig. (2). (**A**, **B**) Scores of BDI, BAI and LSAS related to rTMS treatment for SAD patients.

left OFC, PFC and DLPFC. However, only two controlled studies demonstrated positive effects, more specifically with high-rTMS application, supporting the idea that modulating the right PFC or DLPFC with high-rTMS might be an optimal treatment strategy, due to the possibility of re-establishing the connectivity between an underactive PFC, which is theorized to mediate amygdala activity and amygdala hyperactivity, by increasing PFC activity [47, 56].

However, this rationale contradicts the valence hypothesis. According to this hypothesis, anxiety disorders are characterized by an interhemispheric imbalance, with increased right-hemispheric activity [41, 66]. Thus, would be rTMS a future treatment for social phobia?

With regard to Social Phobia, at the moment, there is only one case report published [67]. In this case report, we found that one session of 1Hz-rTMS over the right ventromedial prefrontal cortex (vmPFC) for 25 min (1500 pulses) improved moderately the anxiety levels and mildly the social skills abilities and that these effects remained after two-months follow-up.

In line with this, we conducted 2 new case reports. The patients A and B were diagnosed with generalized SAD, with comorbidity depression according to DSM-IV-TR. The patient A (23 years old) had 60 mg per day of fluxetine and 2.5 mg per day of clonazepam during two months, was treatment-resistant to cognitive behavior therapy (CBT). The patient B (45 years old) was treatment-resistant to serotonin-specific reuptake inhibitor (SSRI) and CBT. The treatment protocol of rTMS was administered at 1Hz (inhibitory frequency) 120% MT for 25 min (1500 pulses), 3 times per week during 4 weeks over the right vmPFC, structure most consistently activated on SAD [1], representing promising targeted region for rTMS application. Right vmPFC is located near to Fp2 position according to EEG-international 10/20 electrode scalp positioning system. Through this system, satisfactory activation of cortex areas may be reach reliably on a larger scale level [68]. Patients were assessed in baseline, 2 weeks, 4 weeks and after 2 weeks follow-up using the *Beck Depression Inventory* (BDI), *Beck Anxiety Inventory* (BAI) and *Liebowitz social anxiety scale* (LSAS).

In the first case, i.e. patient A (male), we found in baseline the following results: BDI 20 (moderate), BAI 15 (minimal) and LSAS 96 (very severe). After two weeks of treatment, we noted the following results: BDI 10 (minimal), BAI 12 (minimal) and LSAS 71 (moderate). At the end of treatment, we verified the following results: BDI 10 (minimal), BAI 8 (minimal) and LSAS 64 (moderate). On two weeks follow-up, we obtained the following results: BDI 12 (minimal), BAI 8 (minimal) and LSAS 62 (moderate) (Fig. **2A**).

Before rTMS treatment, patient presented very severe level of social anxiety, observed in LSAS, reporting for example, meeting strangers, entering a room when others are already seated (areas most highly rated on LSAS; assessment point level 3). Two and four weeks after rTMS treatment and after 2 weeks follow-up, patient showed large reduction in social anxiety symptoms (areas most highly rated on LSAS; assessment point level 1- minimal) compared to baseline. With regard to BAI, patient presented severe level of anxiety in baseline, reporting for example, unable to relax, heart pounding/racing (areas most highly rated on BAI; assessment point level 2). Two and four weeks after rTMS treatment and after 2 weeks follow-up, patient showed large reduction in anxiety symptoms (areas most highly rated on BAI; assessment point level 1- minimal) compared to baseline. At last, we observed in BDI that patient had moderate depressive symptoms in baseline, reporting for instance, I feel the future is hopeless and that things cannot improve, I feel I am being punished (areas most highly rated on BDI; assessment point level 3). Two and four weeks after rTMS treatment and after 2 weeks follow-up, patient showed large reduction in depressive symptoms (areas most highly rated on BDI; assessment point level 0 - no depression) compared to baseline.

In the second case, i.e. patient B (female), we found in baseline the following results: BDI 27 (moderate), BAI 32 (severe) and LSAS 111 (very severe). After two weeks of treatment, we obtained the following results: BDI 11 (minimal), BAI 6 (minimal) and LSAS 74 (moderate). At the end of treatment, we noted the following results: BDI 9 (minimal), BAI 5 (minimal) and LSAS 69 (moderate). On two weeks follow-up, we verified the following results: BDI 5 (minimal), BAI 1 (minimal) and LSAS 54 (moderate) (Fig. **2B**).

Before rTMS treatment, patient presented very severe level of social anxiety, observed in LSAS, reporting for example, working while being observed, expressing a disagreement or disapproval to people you don't know very well (areas most highly rated on LSAS; assessment point level 3). Two and four weeks after rTMS treatment and after 2 weeks follow-up, patient showed large reduction in social anxiety symptoms (areas most highly rated on LSAS; assessment point level 1- minimal) compared to baseline. With regard to BAI, patient presented severe level of anxiety in baseline, reporting for example, nervous, scared and sweating (areas most highly rated on BAI; assessment point level 3). Two and four weeks after rTMS treatment and after 2 weeks follow-up, patient showed large reduction in anxiety symptoms (areas most highly rated on BAI; assessment point level 0 - no anxiety) compared to baseline. At last, we observed in BDI that patient had moderate depressive symptoms in baseline, reporting for instance, I feel I am being punished, I have no appetite at all anymore (areas most highly rated on BDI; assessment point level 3). Two and four weeks after rTMS treatment and after 2 weeks follow-up, patient showed large reduction in depressive symptoms (areas most highly rated on BDI; assessment point level 0- no depression) compared to baseline.

We suggest that 1Hz rTMS over vmPFC (responsible for emotional regulation) [69], promoted neuromodulation treatment due to its focus on directly targeting the neural circuitry of the disorders. rTMS holds the potential to selectively modulate brain circuitries involved in pathological processes and 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 [9,10]. Thus, it seems that the low-rTMS treatment improved the anxiety and depression levels and social skills performance in a more controlling and therapeutic manner. Despite our positive findings, without a placebo control, at this point these assumptions are merely speculative.

However, after an extensive analysis regarding the findings of rTMS for anxiety disorders [9,10] and based on the slightly observation related to the cases, we now hypothesize that a potential rTMS regime for treating SAD, would be use low-rTMS over the right mPFC and high-rTMS over the left mPFC, which would provoke an transcallosal stimulation of the right mPFC, in order to induce a balance in brain activity. The latter type of stimulation, i.e., high-rTMS, was used as an additional strategy to potentiate the effects of low-rTMS. In addition, the considerations regarding the protocols of depression according to which rTMS should be administered for at least 4 weeks on consecutive weekdays (i.e., 20 sessions) must be taken into account for achieving consistent therapeutic effects. Moreover, an effective control for antidepressant effects should be employed in such studies. This hypothesis raises the exciting possibility that a balanced TMS approach may be fruitful as a potential therapy for SAD.

CONCLUSION

Here, we firstly hypothesized that the application of low-rTMS over the right medial PFC (mPFC; the main structure involved in SAD circuitry) was a potential therapeutic option for SAD. However, after an extensive analysis regarding the findings of rTMS for anxiety disorders [9,10] and based on our findings, we now hypothesize that the application of low-rTMS over the right medial PFC (mPFC; the main structure involved in SAD circuitry) combined with high-rTMS over the left mPFC, for at least 4 weeks on consecutive weekdays, may induce a balance in brain activity, opening an attractive therapeutic option for the treatment of SAD.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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All authors designed, managed the literature searches and drafted most of the manuscript. Flávia Paes, Mauro Carta, Adriana Cardoso Silva, Sergio Machado and Antonio Egidio Nardi wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

ABBREVIATIONS

ACC = anterior cingulated cortex

BAI = Beck Anxiety Inventory

BDI	=	Beck Depression Inventory
CBT	=	cognitive behavior therapy
DLPFC	=	dorsolateral prefrontal cortex
fMRI	=	functional magnetic resonance imaging
GABA	=	gamma-aminobutyric acid
HPA	=	hypothalamic-pituitary-adrenal
LSAS	=	Liebowitz Social Anxiety Scale
mPFC	=	medial prefrontal cortex
OCD	=	obsessive-compulsive disorder
OFC	=	orbitofrontal cortex
PFC	=	prefrontal cortex
PTSD	=	posttraumatic stress disorder
rTMS	=	repetitive transcranial magnetic stimulation
SAD	=	social anxiety disorder
SSRI	=	serotonin-specific reuptake inhibitor
vmPFC	=	ventromedial prefrontal cortex

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Conclusão

Conforme os achados dos artigos 1, 2 e 4, a EMTr é um método não-invasivo relativamente novo e com bom potencial terapêutico para transtornos de ansiedade (Paes et al., 2011; Machado et al., 2012; Paes et al., 2013b). Nesta tese, os estudos 1, 2 e 4 citam de forma aprofundada os resultados da EMTr para transtorno de ansiedade generalizada, transtorno obsessivo-compulsivo, transtorno do pânico, e transtorno de estresse pós-traumático, mostrando que a EMTr pode melhorar alguns dos sintomas associados a esses transtornos (Cohen et al., 2004; Ruffini et al., 2009; Boggio et al., 2010). Além disso, mostram a ausência de estudos de EMTr envolvendo a TAS.

Nos estudos 1 e 2 (Paes et al., 2011; Machado et al., 2012), é abordada a importância do uso da EMTr em modelos animais para o entendimento de como ela age sobre o tecido cerebral e as supostas alterações neurobiológicas subjacentes aos efeitos clínicos observados. Além disso, estudos de ciência básica em nível celular e molecular mostram-se necessários a fim de melhor compreender a regulação da densidade de corrente intracerebral induzida, desvendando quais elementos envolvidos na regulação poderiam servir como potenciais alvos de tratamento (Arias-Carrión, 2008; Platz and Rothwell, 2010).

O estudo 2 discute sobre o risco genético para algumas doenças e que estas poderiam influenciar a resposta dos indivíduos a EMTr (Machado et al., 2012). Pouco se sabe sobre essa questão. Por exemplo, os estudos de Cheeran et al. (2008) e Klein et al. (2006) mostram influência de variantes genéticas na resposta à EMTr. Portanto, um conhecimento profundo sobre variantes genéticas faz-se necessário para prever se os pacientes responderiam ou não à EMTr.

Esta tese é pioneira no estudo da EMTr para o tratamento da TAS. O artigo 3 foi o primeiro caso de EMTr aplicado ao TAS a ser realizado e publicado no mundo (Paes et al., 2013a). Com a publicação subsequente do artigo 4, foi realizada uma revisão aprofundada

sobre o funcionamento cerebral de pacientes com TAS, o racional de tratamento com EMTr para o TAS e dois casos de TAS tratados com EMTr (Paes et al., 2013b). Ambos os casos sugerem que a EMTr tem bom potencial terapêutico para o TAS, embora os resultados sejam muito preliminares.

A EMTr promove modificações na plasticidade cortical, no entanto, estas alterações são transitórias e é prematuro propor estas aplicações como uma opção terapêutica isolada, muito embora a EMTr seja observada como um potencial modulador de neuroplasticidade (Machado et al., 2012; Paes et al., 2013b). Apesar dos resultados positivos observados nos estudos randomizados controlados com outros transtornos de ansiedade (Cohen et al., 2004; Ruffini et al., 2009; Boggio et al., 2010) e nos casos de TAS (Paes et al., 2011; Paes et al., 2013b), vários parâmetros de tratamento, tais como localização, freqüência, intensidade e duração têm sido utilizados de forma assistemática. Assim, a interpretação dos resultados é difícil e pouca orientação é fornecida a respeito de quais parâmetros de tratamento (isto é, a localização de estímulo e frequência) podem ser úteis para o tratamento (Paes et al., 2011). Um ponto de extrema importancia a ser levantado é a falta do uso de exames de neuroimagem funcional nos estudos, que seriam ferramentas fundamentais para mostrar as alterações ocorridas nos circuitos cerebrais causadas pela EMT (Machado et al., 2012). Além disso, com base não somente na teria de Heller et al. (1997), nos estudos de transtornos de ansiedade (Cohen et al., 2004; Ruffini et al., 2009; Boggio et al., 2010) e nos achados relacionados aos três casos, foi elaborada a hipótese de que um protocolo ideal para o tratamento do TAS seria o uso de EMTr de baixa frequência sobre o CPFVM direito e de EMTr de alta frequência sobre o CPFVM esquerdo, o que provocaria um estimulação transcalosa do CPFVM direito, a fim de induzir um equilíbrio na atividade cerebral. A EMTr de alta frequência seria utilizada como uma estratégia adicional para potencializar os efeitos de EMTr de baixa frequência. A ideia

por trás dessa estratégia é o de um reforço no circuito do CPFVM. Com relação aos protocolos da depressão já bem estabelecidos na literatura, a EMTr deve ser administrada durante 5 dias consecutivos na semana, durante 4 semanas (ou seja, 20 sessões), para que possam ser alcançados os efeitos terapêuticos (Lefaucheur et al., 2014; Lefaucheur et al., 2011).

Dessa forma, recomenda-se que novos estudos sejam conduzidos utlizando o protocolo hipotetizado no estudo 4 a fim de verificar a eficácia da EMTr no tratamento do TAS. Vale lembrar que, por mais que sejam relevantes os mecanismos neurobiológicos, a utilidade clínica da EMTr será determinada pela sua capacidade de oferecer aos pacientes com TAS segurança e melhorias substanciais na qualidade de vida em longo prazo.

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APENDICE I – OUTRAS PRODUÇÕES RELEVANTES

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