Review

Candela Zorzo[1,2]
María Banqueri[1,2]
Sara G. Higarza[1,2]
Alberto M. Pernía[3]
Jorge L. Arias[1,2]

Current State of Transcranial Magnetic Stimulation and its use in Psychiatry

[1]Laboratorio de Neurociencias, Departamento de Psicología, Universidad de Oviedo, Oviedo, Spain
[2]INEUROPA, Instituto de Neurociencias del Principado de Asturias, Oviedo, Spain
[3]Área de Tecnología Electrónica, Universidad de Oviedo, Gijón, Spain

Introduction. Transcranial magnetic stimulation (TMS) is a noninvasive brain stimulation technique that could be used as a therapeutic intervention in order to treat psychiatric disorders.

Aim. Reviewing the effectiveness of TMS in the modulation of cognitive functions and also detailing its potential applications in psychiatric treatments.

Development. TMS has been traditionally used for the treatment of a great variety of neurological or psychiatric conditions by modulating the activity in brain areas and networks. Therapeutic benefit has been found in depressive disorders, anxiety, schizophrenia, addiction, and neurodevelopmental disorders as well as in brain damage and neurodegenerative disorders. Moreover, TMS is a technique which offers great tolerance and can be used as complement with other therapies. However, it is not easy to define an optimal treatment for every pathology: the parameters of stimulation are variable, and its effects at the cellular level of the nervous system are not well-known.

Conclusion. While it is true that TMS provides many therapeutic benefits, it requires further investigation. It is necessary to detail the action mechanism of the stimulation and the long-term side effects, if any. This information would allow the design of specific treatment protocols for different psychiatric disorders.

Keywords: Transcranial Magnetic Stimulation, Psychiatry, Depression, Anxiety, Neurodevelopment, Neurodegeneration

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Estado actual de la estimulación magnética transcraneal y sus aplicaciones en psiquiatría

Introducción. La estimulación magnética transcraneal (EMT) es una técnica de estimulación cerebral no invasiva que puede constituir una intervención terapéutica en multitud de trastornos psiquiátricos.

Objetivo. Revisar la eficacia de la EMT en la modulación de las funciones cognitivas, así como detallar las potenciales aplicaciones en tratamientos de trastornos psiquiátricos.

Desarrollo. La EMT ha sido empleada tradicionalmente para el tratamiento de diversas condiciones neurológicas o psiquiátricas debido a la modulación de la actividad de distintas áreas y redes cerebrales. Se observa beneficio terapéutico en trastornos depresivos, de ansiedad, de la esquizofrenia, de adicción, del neurodesarrollo, así como en daño cerebral adquirido y trastornos que cursan con neurodegeneración. Asimismo, constituye una técnica que presenta gran tolerancia y complementariedad con otras terapias. Sin embargo, existen dificultades para definir un tratamiento óptimo según qué patología: los parámetros de estimulación son muy variables y no se conocen en detalle los efectos a nivel celular en el sistema nervioso.

Conclusión. Si bien es cierto que los beneficios terapéuticos de esta técnica son numerosos, precisa de una mayor investigación. Es necesario detallar el mecanismo de acción que induce la terapia, así como los posibles efectos secundarios a largo plazo, si los hubiera. Ello permitiría diseñar protocolos de tratamiento específicos para diferentes alteraciones neurológicas.

Palabras clave. Estimulación Magnética Transcraneal, Psiquiatría, Depresión, Ansiedad, Neurodesarrollo, Neurodegeneración

Correspondece:
Candela Zorzo
Laboratorio de Neurociencias, Departamento de Psicología, Universidad de Oviedo
Plaza Feijoo s/n
33003 Oviedo, Spain
Fax: (+34) 985 10 41 44
E-mail: UO223002@uniovi.es

INTRODUCTION

Magnetic transcranial stimulation (TMS) is a noninvasive brain stimulation technique. It was first used by Barker in 1985[1] and is a therapeutic tool that allows modifying cerebral plasticity outside the skull[2]. TMS is based on the electromagnetic induction principle of Faraday by which energy can be transformed into magnetic fields, and those fields can be transformed into electric energy. Thus, TMS is used to induce electric currents in discrete brain areas, producing selective changes in neurons' electric potential[3,4].

TMS application method can vary according to the researcher or the clinician aims. There are 3 applicable modalities: Simple magnetic transcranial stimulation (sTMS), which delivers a single magnetic pulse over the brain cortex, coupled pulse magnetic transcranial stimulation (cTMS), which delivers two magnetic pulses separated by a variable time interval (depending on the interval's duration, an inhibition or facilitation effect is obtained), and repetitive magnetic transcranial stimulation (rTMS) -on which this review will be focused-, which exerts its effects through a regularly repeated magnetic pulse train[4,5].

Stimulation parameters are very diverse in previous bibliography, and before selecting one of them, the professional has to measure the patient's motor activation threshold to ensure performing TMS treatments below that threshold. Resting motor activation threshold (RMT) is defined as the minimum necessary intensity required in order to generate an evoked motor potential (EMP) in a target resting muscle; it is usually 50 µV in 50% of trials[6]. The procedure starts delivering a reduced intensity, about 35%, in order to increase it gradually by 5% until it evokes an EMP. As of that moment, the stimulus intensity its reduced by 1% steps[6]. The importance of expressing stimulation intensity in clinical studies as RMT is essential due to the existence of interindividual variety of resting cortical excitability[7].

The aim of TMS is to produce relatively small changes in the membrane potential that modulate intrinsic neuronal excitability without directly producing action potentials[8], and these small changes should produce enduring and consistent changes in the neurons[9]. The effects will differ depending on the frequency delivered. rTMS could be high or low frequency. There is some consensus about which low frequency is inhibitory and which high frequency is excitatory. Generally, it has been established that frequencies ≤1 Hz are low, whereas >1 Hz are rated as high. In animal research, the 0.3-1 Hz range is the most frequently used as low stimulation, and 5-20 Hz the most frequently used as high stimulation[7].

The apparatus involves a complex electric system (Figure 1) that would be capable of making thousands of amperes flow in milliseconds towards a stimulation coil which, in turn, will generate a magnetic field (Figure 2). In particular, a central unit is needed to indicate the amount of current and to synchronize its delivering, capacitors that accumulate electric charge, wiring, and a stimulation coil that could vary. The geometry of the stimulation coil will determine the intensity, stimulus penetration, and stimulated area focality. In this way, the circular coils would stimulate broad brain cortex regions, while eight-shaped coils could be more focused. These differences are due to the coils' configuration –in the eight-shaped one, it is two joined circular coils- which allows each coil to transport the current in opposite directions, producing an electric field sum where they join[10–12]. Therefore, stimulation focality depends on the coil diameter, and it is more focal when the diameter is lower[6]. The extension of cortical activation depends on multiple factors, like coil shape, pulse-generated wave (mono or biphasic), and, of course, the coil's position over the skull[13].

Ultimately, the parameters used will determine the results obtained in TMS treatment. Therefore, it is essential to suit the frequency, intensity, pulse number, time interval between trials, and session number. Stimulation frequency oscillates between 1 and 60 Hz, but the most frequently used range from 1 to 10 Hz, depending on the pursued goal[14]. Pulse intensity is very variable, oscillating from 0.7 to 3.4 Teslas (T)[4], with the most common ranging between 1 and 2 T[6]. Regarding TMS pulse number, these could vary from 15 to 2400[14]. Time interval between trials is also variable, the most frequently used intervals range between 10 and 30 s[15]. Finally, the number of required sessions, which depends on the medical condition and its severity in clinical

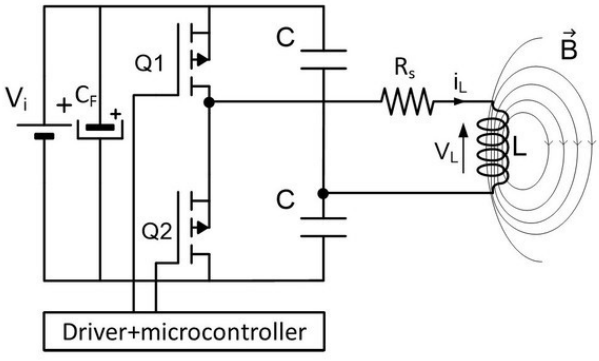

Figure 1 — *Schematic diagram of the electric system that feeds the coil in a magnetic stimulator. L is the emission point*

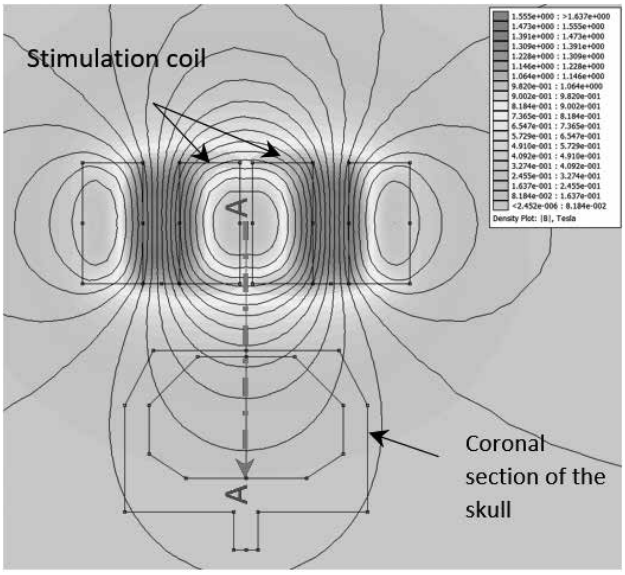

Figura 2 — *Theoretical distribution of induced magnetic fields by a stimulation coil. Line A-A indicates the penetration power that allows it to penetrate skull and encephalon.*

practice, and on the experimental goals in cognitive neuroscience.

Magnetic fields' application, which is capable of inducing electric currents in nervous tissue and the subsequent selective changes in neurons' potential[4], has allowed distinguishing the therapeutic rTMS potential in the psychiatric field[16]. Specifically, rTMS can increase or decrease cortical excitability, which could be useful in diseases in which there is hypo- or hyperfunctionality of some cortical network, or where cortical excitability induces neural network reorganization[6]. In this way, rTMS applied in a specific brain area can exert an effect in another brain region through neural connections. This effect is also found in other noninvasive therapies, like low-level light therapy, producing a beneficial effect in certain pathologies such as minimal hepatic encephalopathy[17]. Finally, we highlight that rTMS has a well-established security profile and is capable of modulating brain activity without surgery, anesthesia, or convulsive induction[4].

Characterizing the brain networks and cell functioning that sustain cognitive and emotional functions, defining the nature and causes of pathologies, and identifying the most effective treatments is particularly relevant. In this review, we focus on rTMS effects in depression, anxiety, schizophrenia, addiction, and neurodevelopmental pathologies, and also the possible intervention in patients who show brain damage or pathologies evolving with neurodegeneration. An optimal treatment can improve the quality of life in these patients, not only in clinical aspects but also in social and professional areas.

TMS PSYCHIATRIC USE

Depressive disorder

Major depressive disorder is found within the classification of mood disorder, a chronic and recurrent condition that produces clinical discomfort and deteriorates social and work performance or other relevant areas for the patient[18]. It is sometimes also resistant to conventional treatments.

The first research on rTMS and depressive disorder took place in the 1990 decade. Different research groups started to apply magnetic fields on patients' brain cortices, the most frequent delivery was to the left dorsolateral prefrontal cortex (dlPFC) (5-20 Hz; 5-20 sessions)[19–23] and also low frequencies to the right dlPFC (1 Hz; 10 sessions)[24]. Although the stimulation parameters were variable (frequency, intensity, and days of treatment), the researchers started to observe clinical improvements in patients' mood, showing a decrease of symptoms evaluated with diverse scales such as the Hamilton Depression Rating Scale (HDRS)[19,24–26]. Some meta-analyses in the field concluded that rTMS is useful for the remission of depressive disorder[27–29] but some studies showed the superiority of electro-convulsive therapy (ECT) when compared with TMS[30].

Regarding the benefit in diverse cognitive functions — which could be altered due to depressive disorder—clinical improvement has been found in working memory[20], episodic verbal memory, language, and visuospatial function[21]. Additionally, some interesting results reveal correlations between neuropsychological batteries and neurophysiological findings, suggesting a plastic remodeling of synaptic connections induced by rTMS treatment[22].

Moreover, animal model research shows that rTMS can increase postsynaptic excitatory potentials after long-term potentiation induction, revealing an antidepressive effect after a short treatment period with high frequency[31]. In addition, this kind of intervention is related to the increase of hippocampal cell proliferation and neurotrophic factors, which suggests a relation with neuroplasticity[32]. Lastly, beneficial effects have been found in coping strategies, which become more active during the forced swimming test[33], which could be emulating part of the depressive symptoms found in human population.

Therefore, we can conclude that rTMS has become a promising alternative therapy for depressive disorder treatment. There is some consensus about the optimal administration method, with the delivery of high frequencies over the left dlPFC being the most frequently suggested[27,34,35]. However, the neurobiological mechanisms of this rTMS antidepressive effect are not yet well known.

Anxiety Disorders

Anxiety disorders are one of the most common psychiatric disorders. Although there are effective psychotherapeutic and psychopharmacological interventions, a considerable number of patients do not respond to standard clinical treatments[36]. As rTMS can modulate cortical excitability focally and noninvasively, it could be considered as a possible therapeutic method for anxiety disorders. Due to the existence of a broad classification of anxiety disorders, some of the subtypes will be considered in this review.

Post-traumatic stress anxiety disorder (PTSD) is a chronic psychiatric disorder that can occur after a traumatic event. One third of the patients suffering PTSD are refractory to usual treatments[37]. PSTD could lead, among other alterations, to hypoactivation of the prefrontal cortex (PFC)[38]. rTMS could restore the PFC to normal activity. The first study that researched the effects of rTMS on PTSD was based on a low frequency application (0.3 Hz; 1 session) in both hemispheres of the motor cortex, and produced a decrease in the central symptoms of the disorder, such as avoidance, somatization, or anxiety[39]. In addition, improvements in physiological hyperactivation have been recently described[40].

Generalized Anxiety Disorder is characterized by persistent and excessive worry as well as deficits in the regulation and identification of emotional experiences. rTMS preliminary studies (1 Hz; 30 sessions) applied to the right dlPFC suggest that it could improve some of the disorder's symptoms[41], modifying the neural excitability in the application area[42]. Using the same protocol, improvements in emotion regulation, both post-treatment and at a 3-month follow-up, have also been found[43]. Moreover, different stimulation parameters from those indicated above (20 Hz; 25 sessions) applied to the right dlPFC showed a decrease of anxiety symptoms assessed with the Hamilton Anxiety Scale (HARS) by at least 50% of the total score, with benefits remaining up to 4 weeks after treatment[44].

Panic disorder is characterized by the presence of unexpected and repeated periods of intense fear followed by physical symptoms, in addiction to fear of having future episodes of panic. Preliminary studies show that rTMS application (1 Hz; 10 sessions) to the right dlPFC in panic disorder comorbid with major depression can result in clinical improvement[45], and benefits are also found when stimulation is applied both to the right and the left dlPFC[46]. Therefore, it is suggested that rTMS could help to normalize altered brain activity in patients affected by this disorder[47].

Social anxiety disorder—also called social phobia—is characterized by a significant fear and avoidance of social situations[18], and benefits can be found after the application of rTMS. Taking into account that some brain areas such as the medial PFC (mPFC) and the amygdala play an important role in the disorder[48], one session of 1 Hz frequency of rTMS to the right ventromedial PFC was reported to produce a decrease in anxiety levels as well as an improvement of social skills, with the benefits remaining up to two months after stimulation[49,50]. In this case, different neuropsychological scales were used: the Beck Depression Inventory (BDI), the Beck Anxiety Inventory (BAI), and the Liebowitz Social Anxiety Scale (LSAS). However, taking into account the rTMS findings in anxiety disorders, the hypothesis of low-frequency application to the right mPFC in combination with high frequency to the left mPFC[50] is suggested.

Finally, interventions in obsessive-compulsive disorders (OCD) may also show therapeutic benefits. OCD is characterized by the presence of obsessive thoughts and / or recurrent compulsive acts, and the participation of both cortical and subcortical structures is suggested. Specifically, hyperactivation within the cortico-striatal-thalamus-cortico circuits, including prefrontal and orbitofrontal cortices, motor area, striatum, globus palidus, and thalamus could be responsible for the symptoms of OCD[51]. Due to the dysfunction of cortical regions, some researchers expected that the rTMS approach to the PFC could help to decrease the symptoms of OCD. Consequently, the first investigations in the field observed reductions in compulsive impulses[52] and clinical improvements in patients with OCD and Tourette's syndrome[47]. Recently, rTMS applied to the supplementary motor area (1 Hz; 30 sessions)[53] or to the dlPFC (1 Hz; 10 sessions), either in the right hemisphere[54] or in both hemispheres[55], showed a reduction in obsessive-compulsive scores. However, other studies did not find these benefits[56]. Although these studies are promising, more research is needed focusing on the evaluation of the efficacy of rTMS in OCD as well as a clarification of the optimal stimulation parameters.

Schizophrenia

Schizophrenic disorders are one of the most invalidating and costly diseases in the world. In this classification, the DSM-V (Diagnostic and Statistical Manual of Mental Disorders) includes 13 types of psychotic disorders. One of the main problems in clinical practice is the resistance to treatment, occurring in 20-30% of patients who suffer a psychotic disorder[57]. Although rTMS has been proposed as a

novel therapy in schizophrenia, the known complexity of this disorder does not allow us to confirm its effects on the disease as a whole, but to refer to its efficacy in some of the symptoms[58]. Thus, the therapeutic effects in schizophrenia can target both positive and negative symptoms or the cognitive alterations[7,59] that may be present in this pathology. In reference to positive symptoms, one of the most commonly studied are the verbal auditory hallucinations. Low-frequency rTMS applied to the left temporoparietal cortex (1 Hz; 4-10 sessions) could inhibit the aberrant activation that causes certain types of hallucinations[60-63], although other researchers have found no difference between stimulation of the right temporoparietal cortex compared to the left[64]. We think that rTMS could revert the hyperfuncionality of the language areas involved in hallucinations because the cerebral blood flow in the primary auditory cortex, the Broca area, and cingulate gyrus decreases, correlating with the reduction of verbal auditory hallucinations[65]. There are promising results in the research of the treatment of negative symptoms[28]. rTMS applied to the left dlPFC (10 Hz; 15-20 sessions) reduces the severity of the negative symptoms as assessed with the Scale for the Evaluation of Negative Symptoms (SANS)[66,67] and with the score of negative symptoms of the Scale of Positive and Negative Syndrome (PANSS)[67], as well showing benefits in facial affect recognition[68]. Finally, and referring to altered cognition, several researches describe the improvements in working memory after a bilateral application to the dlPFC (20 Hz; 20 sessions)[69], although other studies do not find this cognitive benefit[70].

Therefore, rTMS applied in schizophrenia disorders is a promising technique that could lead to improvements both in the positive, negative, and cognitive symptoms affected, with some consistency in the action protocol when referring to the negative symptoms[28].

Neurodevelopmental disorders

Neurodevelopmental disorders are characterized by the presence of several deficits in different cognitive and non-cognitive abilities, with the first symptoms appearing during childhood[18]. rTMS can be useful in Tourette's syndrome and Autism Spectrum Disorder (ASD)[3], both alterations classified under neurodevelopmental disorders.

rTMS (1 Hz; 20 sessions) applied to the supplementary motor area in Tourette's syndrome produces a reduction in the severity of the tics for at least 6 months[71] , finding similar results with a lower number of sessions (1 Hz; 10 sessions)[72].

In reference to ASD, it affects approximately 1% of the population[73]. However, there is no clear opinion about its etiology, although it is generally accepted that the symptoms arise as a result of abnormal neuronal development[74]. rTMS could induce a modulation of the cortical excitability in specific neuronal circuits[75]. In addition, the bilateral application to the dlPFC can lead to an improvement in tasks depending on executive functions (altered in ASD) such as working memory or cognitive flexibility[76].

Until now, the projects that have studied rTMS as a therapeutic tool in ASD have focused on samples without intellectual disability[77], finding benefits in relationships and anxiety after a bilateral application to the dorsomedial PFC (dmPFC) (5 Hz; 10 sessions)[78]. Regarding the population with intellectual disability, rTMS has been applied to the left premotor cortex, finding an improvement in eye-hand coordination (previously altered) after an application of 3-10 sessions with 8 Hz frequency[79].

Finally, low-frequency stimulation (0.5 Hz; 6 sessions) to the dlPFC shows a normalization in evoked potentials and electroencephalographic activity of gamma frequency induced in frontal and parietal areas, as well as a reduction of repetitive behavior[80,81]. Bilateral rTMS to the dlPFC with different parameters (1 Hz; 12 sessions) shows similar results[82].

The results presented above allow us to confirm the promising use of rTMS as a possible intervention in some symptoms underlying neurodevelopmental disorders, taking into account the neuroplasticity that characterizes the pediatric population, and, consequently, the opportunity this population provides for the modulation of the neuropathology[3,5]. Applications of rTMS in ASD would not be restricted to therapeutic perspectives, but could also help in the diagnosis and knowledge of the physiological mechanisms, based on the study of cortical excitability and inhibition[75]. However, as most rTMS studies have been performed in adulthood, it is important to underline the differences that could appear in adolescent and child interventions. Therefore, it is essential to assess the nervous system's maturational status in terms of intracortical synapses and myelination.

Addictive disorders

Substance abuse disorders are characterized by a hypoactivation of the PFC[83]. Nowadays, pharmacological and cognitive-behavioral therapies have limited efficacy on relapse in substance abuse disorders[59]. It is known that the dlPFC plays an important role in the inhibition of reward circuits; thus, the application of focalized rTMS could show promising results in this field. In this respect, there are some studies that reveal the efficacy of rTMS in the reduction of nicotine consumption and craving after delivery to the PFC and the insula on a bilateral basis (10 Hz, 13 sessions)[84], and also for cocaine consumption by targeting the left dlPFC (10 Hz, 8 sessions)[85] or for alcohol consumption, to the right dlP-

FC (10 Hz, 10 sessions)[86]. However, there are not many studies in the field, so the need for deeper research is suggested in order to correctly confirm the use of rTMS as a potential treatment for substance abuse disorders. A good understanding of rTMS effects in addictions could be extrapolated not only to substance abuse disorders, but also to other addictive disorders not dependent on substances.

Brain damage

Cognitive abilities like perception, memory, or attention can be modulated by rTMS, which could result in a promising alternative in neurophysiological research and also in intervention therapy after brain damage. rTMS can induce magnetic currents that depolarize neurons in particular brain regions, which could be useful in the manipulation of cortical networks that alter cognitive performance[87]. The first studies in this field emerged back in the 1990s and they showed an improvement in memory and reaction speed[88] as well as in attentional processing[89]. Likewise, the beneficial effect of rTMS has been observed in working memory, contributing to item codification tasks[20,90].

Brain damage derived from cerebrovascular accidents or head traumas causes multiple consequences, including cognitive function impairment. Some research using animal models has shown that rTMS can increase neurogenesis in the hippocampus[91], raising the possibility that this increase could affect BDNF (brain-derived neurotrophic factor) signaling[92,93], resulting in a neurorehabilitation effect after a cerebrovascular accident (CVA)[93]. The first studies that applied rTMS to CVA were carried out in 2005, by targeting the motor cortex (M1) of the healthy hemisphere (1 Hz; 1 session). An improvement of reaction speed in the paralyzed hand was observed[94], also when the protocol lasted for 5 sessions[95]. Regarding cognitive function, even though in 2005 a pilot study informed about the positive effects on the executive functioning after a 10-Hz rTMS session to the left dlPFC in patients with cerebrovascular disease, these improvements were only evaluated by the Stoop test[96]. Hence, apart from research using animal models, to our knowledge, there are few studies about the effects of rTMS on cognition in patients with brain damage.

Neurodegenerative disorders

In this last section, we will provide a general vision of the importance of rTMS delivery in multiple neurodegenerative disorders, highlighting Alzheimer's disease (AD) and Parkinson's disease (PD).

AD is characterized by memory loss, language impairment, difficulty in performing simple tasks, and disorientation. Therefore, it severely impacts on the quality of life of the people affected. High frequency rTMS (20 Hz) applied bilaterally to the dlPFC improves language abilities, as evaluated through naming and phrase understanding tasks[97-99]. Furthermore, when combined with cognitive training, rTMS (10 Hz; 54 sessions) delivered bilaterally to the dlPFC and to the somatosensorial association parietal cortex is capable of improving the score in the cognitive assessment scale of AD (ADAS-Cog)[100]. These findings suggest that rTMS can affect the brain's intrinsic capacity for restoring or compensating the damaged function, representing a new and useful tool for cognitive rehabilitation[97,101].

Although there is some information about the action mechanism of rTMS in animal models of AD, as a greater expression of synaptic proteins has been found in the hippocampus associated with an improvement in learning and memory functions[102], there are some questions that remain unsolved. Thus, some authors raise the possibility that the mentioned therapy improves cognitive functions associated with dementia, acting directly on the targeted brain area and its circuits[103]. Hence, it seems that rTMS could play a role in the increase of cortical excitability in AD[13].

PD includes an alteration of cortical inhibition[13] as a consequence of the death of dopaminergic neurons in the substantia nigra. Although pharmacological therapy has a good prognosis, long-term efficacy is usually reduced. rTMS together with training improves motor function in patients with PD[104]. Additionally, an increase of dopaminergic levels was noted after the magnetic stimulation treatment[105,106], suggesting a neuroprotective effect of the therapy[106]. There is abundant bibliography about the effect of rTMS on motor function[10], but this is not the case for cognitive function. To our knowledge, only one study has indicated that rTMS to the left dlPFC (10 Hz; 10 sessions) can produce cognitive amelioration in humans[107], which leads us to request, once again, further research in this field.

CONTROVERSY OVER THE USAGE OF RTMS

As mentioned, TMS is a promising treatment for multiple psychiatric disorders. The main difficulty is to define optimal treatments (identifying the parameters, the place of delivery, and the necessary doses[58]), as the situation differs in diverse pathologies. Although TMS has been tested recently in a great variety of mental disorders, some of them have been extensively described, whereas others are still at preliminary phases and show large heterogeneity. Furthermore, there is consensus concerning delivery only in some of these disorders. For example, in the treatment of major depression or in the negative symptoms of schizophrenia[34], high frequencies to the dlPFC are considered optimal. How-

ever, other psychiatric disorders have no established action protocol.

The modification of TMS parameters can lead to a great variability of responses. The use of low frequencies (≤1 Hz) and a continuous rate (at least 300-900 pulses) are associated with sustained inhibition and excitability suppression, whereas high frequencies (>1 Hz) and discontinuous rates cause the opposite effect, an increase of excitability[37]. Therefore, the choice of TMS parameters defines an activating or inhibiting response. In addition, TMS presents an accumulative effect[108] thus, the number of doses and the time of delivery will have a decisive impact on the stimulation. Although the long-term effect of TMS[58] is not known with certainty, it has been shown that it declines over time and that the repetition of stimulation sessions in intervals of under 24 hours can induce long-term changes in cortical activity[109].

The ongoing maintenance of the TMS delivery characteristics, even if they had been successful in the treatment of a particular pathology, is not a guarantee of success. The lack of replicability in the usual research is attributed to interindividual differences, the most significant of which are age, gender, genetics, skull-cortex distance, white matter connectivity, individual levels of excitability, and neurophysiological characteristics[7,93]. The effect of the usual medication for the pathology on the TMS treatment also has to be taken into account, as has already been shown[102].

The response is also determined by the excitation levels prior to stimulation[93]. It has been described that the delivery of excitatory frequencies first affects the systems that are on a lower level of excitation, whereas the inhibitory frequencies exert their effects initially on the systems that present a higher excitatory level[103]. Hence, the excitability status determined by the execution of the task before or during the stimulation will regulate the magnitude and direction of the modulator effects[93].

In spite of being a widely used technique, TMS raises some questions about its action mechanism. The effect at the cellular level in the nervous system is not known. Neurons use electric signals to communicate; thus, the interference of the stimulation over the target area can produce consequences that are not always controllable[110]. It has been shown that TMS can positively induce neurogenesis[111]. This type of stimulation can affect the neurons through the activation of the dendrites, but multiple physiological factors, such as the distribution of cells in the cerebral cortex, their communication, and excitability, influence the stimulation process[110]. Likewise, despite that some studies have focused on the effect of TMS on glial cells, its mechanisms have not been elucidated[14].

Undoubtedly, this technique requires more research in order to describe the action mechanisms of TMS from the molecular perspective to neural networks, thereby leading to the design of specific action protocols for each disorder, maximizing the therapeutic potential and minimizing the possible side effects.

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CONFLICT OF INTERESTS

Authors declare the absence of conflicts of interest

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