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Special article

Advances in transcranial magnetic stimulation (TMS) and its applications in resistant depression

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ABSTRACT

Transcranial magnetic stimulation (TMS) is a non-invasive method of brain stimulation that is receiving increasingly attention for new clinical applications. Through electromagnetic induction cortical activity can be modulated and therapeutic effects can be achieved in a variety of psychiatric and neurological conditions. According to the World Health Organization (WHO) depression is the most disabling disease in the world and 350 million people suffer from depression globally. Major depression is the most common disorder to be treated with TMS and the first mental disorder for which TMS received approval from the US Food and Drug Administration (FDA). We here introduce the basic principles of TMS, discuss the latest data on safety and side effects, and present various TMS treatment protocols as well as treatment response predictors in major depressive disorder.

KEYWORDS: Repetitive Transcranial Magnetic Stimulation (rTMS), dorsolateral prefrontal cortex, major depressive disorder, cognitive neurosciences, rTMS protocols.

Introduction

Transcranial magnetic stimulation (TMS) is based on the principles of electromagnetic induction and was first introduced by Barker et al. in 1985.[1] TMS is transcracially and thus non-invasively applied through the intact skull using an electromagnetic field placed over the patient's head. The TMS coil creates a changing electric field, which in turn induces a magnetic field that passes the skull painlessly. The magnetic field in turn induces a changing electric field in the brain, which leads to the stimulation of neurons. Repetitive TMS (rTMS) has been shown to increase or decrease cortical excitability in both the directly targeted and indirectly connected remote brain regions, including regions that regulate cognition and emotion.[1,2] It is an evidence-based treatment option, accepted by the American Psychiatric Association, the Canadian Network for Mood and Anxiety Treatments, and the World Federation of Societies of Biological Psychiatry. In 2008, it received approval from US Food and Drugs Administration (FDA) as a treatment option for patients

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suffering from treatment-resistant major depressive disorder (MDD) and has been adopted into clinical practice in a growing number of countries worldwide.[3] In general, its effectiveness is higher when applied at the acute state of the disease, in relatively young individuals (less than 65 years old), at limited levels of treatment resistance (one or two unsuccessful medical interventions) or in cases of partial treatment response.[4]

History

The course from discovery of modern TMS to the establishment as a treatment in clinical practice has been a long and winding road. Followed by the discovery of electromagnetic induction by Faraday and Henry,[5] whereby electrical fields E can be converted into magnetic fields B, and magnetic fields B can be converted into electrical energy, it was now possible to stimulate the nervous system painlessly by exposing patients to changing magnetic fields, and the first successful attempts achieved within the time period of 1896–1910 by d' Arsonval,[6] followed by Beer and Thompson.[7–10] The difficulty now was in the creation of high intensity current and rapid change of a field so as to induce a physiological activity in the brain. It was not before 1985 that they finally succeeded to develop the stimulators that could produce the required discharge to generate a magnetic field capable to induce current in the cortical tissue. This achievement by Barker et al, however, marked nothing less than the beginning of the use of modern rTMS in brain research and clinical practice.

Major depressive disorder

Major depression is the most thoroughly studied of the potential psychiatric application of TMS.

Treatment-resistant depression (TRD) is defined as a major depressive episode that does not respond to at least two antidepressant therapies, given in adequate doses and for a sufficient period.[11,12] A significant percentage of patients with MDD, i.e., 10–30%,[13] do not respond to medication[14,15] and 30% of these patients have been shown to not respond to any treatment.[11,16] About 10% of patients are chronically resistant to several psychopharmacological interventions, even when adhering to treatment guidelines.[17] TRD represents a dilemma for health care providers, as it has been shown to negatively affect the patient's quality of life, physical health, functionality, social life and work performance.[12,18] It has also been shown to reduce a person's life expectancy by increasing the risk of cardiovascular mortality[19] as well as suicide and self-harm.[20]

Major depressive disorder and rTMS

The dorsolateral prefrontal cortex (DLPFC) has been the main target for neurostimulation with rTMS in depression. A substantial body of literature supports the theory that mood is regulated by a network of brain regions (including the prefrontal, cingulate, parietal and temporal cortical regions as well as parts of the striatum, thalamus and hypothalamus) and that focal lesions in this network (from infarction, tumor or transient disruption) can result in mood disturbances. Furthermore, patients with depression demonstrate alterations in cerebral blood flow (CBF) and metabolism in those regions.[21–23] The first rTMS mood and depression studies selected the DLPFC as a region within this network best accessible to TMS and highly connected with other key nodes in the network, such as anterior cingulate regions.

In addition to its easy accessibility, there was also initial evidence from functional neuroimaging studies suggesting a reduction of metabolic activity in specific brain areas of depression patients, most notably within the left prefrontal cortex.[24.25] The theory was reinforced with observations such as the propagation effects of TMS to surrogate physiological endpoints consistent with potential antidepressant action,[26] the delay of onset of REM sleep,[27] and the normalisation of hypothalamic pituitary adrenal axis function,[28] when applied to human experimental models; the behavioural effects similar to those of antidepressant when rTMS was applied to animal models[29] and the proven changes in neurochemical and cellular targets that are implicated in antidepressant action.[30]

The state-of-the-art depression TMS therapy now uses rTMS to deliver a rhythmic train of magnetic pulses with a certain frequency in Hertz (Hz) to the left or right DLPFC in order to increase depression network activity and connectivity. This rTMS protocol affects the targeted brain regions even beyond the period of stimulation[31,32] with lasting effects on excitability that can either be (on average) inhibitory (1 Hz) or excitatory (10 Hz) in nature, depending on the precise parameters of the rTMS protocols. It has been suggested that rTMS protocols engage synaptic plasticity mechanisms, such as long-term potentiation (LTP) and long-term depression (LTD), to achieve these lasting modulations of neuroplasticity.[33–35] In the last three decades, TMS has slowly but surely worked its way into the established range of treatment options for depression, with TMS clinics sprouting globally and TMS machines finding their way into the offices of experienced psychologists and psychiatrists. Depression has been associated with aberrant connectivity in several frontostriatal and limbic brain networks, and in particular the subgenual anterior cingulate cortex (sgACC). Currently, the gold standard TMS approach to treat depression is daily high-frequency repetitive TMS (HF-rTMS) applied to left dorsolateral prefrontal cortex for several weeks. This depression TMS protocol is assumed to 'stimulate' the left dorsolateral prefrontal cortex (lDLPFC), and importantly, also affect connected limbic system regions, among

which the connection between the DLPFC and the sgACC seem most relevant in the treatment success of TMS.[36–38] Response rates and remission rates vary between clinical trials, but conservatively estimated, approximately 30–40% of TRD patients respond to this TMS treatment.

rTMS versus ECT

Electroconvulsive therapy (ECT) is a well-established depression treatment, which is now considered the "gold standard" in the therapy of treatment-resistant depression. Research suggests that it is superior to pharmacological therapy.[39,40] Clinical indications for the application of ECT are the resistance to pharmacotherapy, melancholic features, catatonic symptoms, the onset of the disease during the peripartum period, the need for rapid response to treatment and suicidality.[41,42] Since 2008, rTMS has been an FDA-approved treatment for treatment-resistant MDD. ECT's effectiveness in MDD has been shown to reach 75% within the first 2 weeks,[43] while in psychotic depression the effectiveness reaches 90%.[44] Despite its high efficacy rates, it is accompanied by many side effects, most importantly memory loss, and its application requires general anaesthesia of the patient.[45] In contrast, rTMS, although a relatively new treatment, presents itself with a much safer profile. An important factor is the absence of the need for anesthesia of the patient and its application does not require the induction of seizures.[45] Although a seizure is a serious side effect of this treatment, the risk of occurrence appears extremely small.[46] Moreover, an important difference between the two therapies is the absence of a negative effect of rTMS on the cognitive abilities of the patient.[47] In fact, several studies even indicated that the application of the treatment can improve the patient's memory and cognitive performance.[48–50] Despite the predominance of rTMS both in the treatment process and in the profile of side effects, ECT continues to be the most effective and acute treatment for treatment resistant MDD.[40,51,52] However, rTMS constitutes an excellent alternative in the treatment of treatment-resistant depression, in patients who do not tolerate side effects or who do not want to receive an ECT treatment. Most certainly, it seems reasonable to first try rTMS before considering ECT, especially when comparing the high tolerability, safety profile, and good efficacy of rTMS for these patients. A systematic review and meta-analysis and by Ren et al. found ECT and high frequency rTMS to be equally effective in non-psychotic resistant depression.[53]

Safety: Precautions and side effects

A number of TMS techniques are nowadays used for routine diagnostic application,[54] and a variety of safety articles have been published by International Federation of Clinical Neuropsysiology.[54,55]

Adverse effects

rTMS is generally a safe treatment method with few side effects. The most common side effects are a transient headache that usually does not last long and responds to simple analgesics, local discomfort in the stimulation area, dizziness and ipsilateral lacrimation. Rarely acoustic trauma and, very rarely, generalized seizure and hypomanic shift are reported.[51,56,57] There are some rare reports of triggering psychiatric symptoms after the patient is exposed to rTMS (psychosis, anxiety, irritability, suicidal ideation), but there is yet no clear proof of the relation with the treatment and when they do occur, they are usually transient and resolve spontaneously after discontinuation of treatment or when indicated pharmacotherapy is given.[58–61]

Seizures

Induction of seizures is the most severe acute side effect of rTMS. It is a side effect that can occur in any person and with the application of any therapeutic frequency, but it is usually occurs when the application of the treatment exceeds the therapeutic limits. Seizures may happen due to an over-synchronized secretion of neuronal groups in the grey matter, as a result of the predominance of stimulant over inhibitory activity in the synaptic cleft.[54] By 2020, there were only 41 references in the literature on seizures during treatment[62] and the risk, compared to induce seizure from the use of antidepressants is relatively low.[63] The overall risk of seizure is estimated to be less than 1 in 30,000 treatment sessions (<0.003%) or less than 1 in 1,000 patient exposures (<0.1%).[64] Special attention must be given when therapy is applied to patients receiving medication which reduces the seizure threshold. However, one must also keep in mind that a syncoptic episode can be misinterpreted as an epileptic seizure.

Acoustic trauma

Although the application of treatment can bring positive results in cases of patients with auditory hallucinations,[65,66] hearing loss or chronic tinnitus,[67–69] auditory trauma, usually as an acoustic noise, can be one of its side effects. This can be caused by the intensity of sound emanating from the discharge of magnetic coils, which can be potentially greater than 120 dB of sound pressure level. The amount of sound reaching a patient ear can of course vary and this is due to changing parameters, such as the type of coil, the size of the ear canal, the number and the repetition frequency of TMS pulses, the position and distance of the coil from the meter.[70] Moreover, since the TMS coil typically rests on the head, sound can be conducted through the skull bone and contribute risk which is not quantified with conventional sound measurements.[70,71] After exposure to the TMS stimulus, few adult participants have experienced transient increases in auditory thresh-

olds.[72,73] The actual risk increases when a stimulus applied over the auditory cortex, near the ear, especially when hyperacusis was already present before rTMS[74] and if patient is being treated with ototoxic medications (aminoglygoside antibiotics and platinum-based compounds).

Hearing safety recommendations

The risk of hearing problems can be prevented with the use of well-fitted and approved hearing protection (earplugs or earmuffs) by patients and rTMS operators, by referral for auditory evaluation of any individual complaining of hearing loss, tinnitus, or aural fullness following rTMS and by taking into account the risk and benefits ratio of individuals with pre-existing noise-induced hearing loss or concurrent treatment with ototoxic medications before rTMS.[54,71] To individuals who have an implanted vagal nerve stimulation device, a single-pulse TMS can be safely applied,[75] but patients with cochlear implants should not undergo rTMS.[54]

Safety for operators

In general, there are no specific reports of adverse effects of rTMS in operators, even in cases they are being exposed to magnetic fields for several hours daily, even for years, although this field needs further investigation in the coming years.[54,76] Safety issues until today are seldom addressed for operators. Guidelines for occupational levels of exposure to electromagnetic fields have been proposed by the International Commission on Non-Ionizing Radiation Protection and by Directives from the European Parliament.[54]

Approved TMS treatment protocols

Based on the concept of frontal asymmetry of cortical activities in depression, two main lines of research have been developed for the treatment of depression with rTMS: LF stimulation (inducing neural inhibition) on the right DLPFC (presumably hyperactive in depression), HF stimulation (putatively inducing neural excitation) on the left DLPFC (presumably hypoactive in depression), or a combination of the two.[77–79]

Conventional rTMS: low and high frequency

In the last ten years the number of rTMS studies including clinical trials has grown impressively; a Medline search (October 2019) using "TMS" or "rTMS" or "Transcranial Magnetic Stimulation" as keywords identified 14,000 papers of which about 1,400 included the term "clinical trial". The imagination of researchers in designing new combinations of frequency, intensity, train duration, number of pulses per day, number of sessions day/week, duration of a standard course of therapy, type of coil, and number and location of brain stimulation sites has been enormous. For these reasons, it is unrealistic to categorise all these variables into new tables.

Patterned rTMS: Theta Burst stimulation (TBS)

The majority of TBS papers have used the parameters originally described by Huang et al (50 Hz bursts of 3 pulses repeated at 5 Hz; stimulus intensity of 80% AMT).[33] To the best of our knowledge, there has only been one seizure reported using these parameters.[80] The other seizures reported using TBS have used parameters that exceed these levels.

Parameters that Predict a Clinically Significant Response to rTMS

The range of effectiveness observed in the published reports is strikingly wide. There are some factors that seem to play a relevant role on response rates.

Protocols

The length of the treatment, this is the number of sessions provided, is extremely heterogeneous in literature. Several reports[28,81–84] highlight the relevance of rTMS long treatment courses. Furthermore, stimulus intensity seems to be crucial, as studies applying high intensity TMS, around 100% to 110% of the motor threshold,[28,58,78,82,85–88] seem to report better results than those employing 80% to 90% of the motor threshold intensity.[28,78,81,89,90] Finally, the number of rTMS pulses per session is also important. Studies in which 1200 to 1600 pulses were delivered in each session[28,78,83,86,88,89] were more successful in either terms of remission rates or net mood response than those applying 800 to 1000 pulses a day.[82,91]

Patient characteristics

Some studies[82,92] have observed that older patients responded less effectively to rTMS. The aging brain presents with a greater degree of cortical atrophy and the enlargement of the sulci may play a role. A greater amount of cerebrospinal fluid collections probably diminishes the focality of the treatment in this patient population. Holtzheimer et al[93] also noted a significant negative correlation between length of the current depressive episode and response to rTMS. Furthermore, patients with psychotic depression often have shown lower response rates.[81] Preliminary evidence indicates that a previous response to rTMS increases the response rate for new treatments when relapses occur.[94]

Cortical excitability changes

Cortical excitability changes have been addressed by Maeda et al[95] in both healthy and depressed subjects. TMS paired-pulse studies measure intracortical inhibition

or facilitation. Hence, they allow having a reliable correlate of the modulatory effect of TMS in the cortex.

Imaging studies

Imaging studies with SPECT[96] and PET[97] can also predict whether patients may be better responders to TMS. The baseline activity in the inferior frontal lobe is higher in patients that tend to respond to rTMS.[96] Conversely, hypometabolism in both temporal lobes, the cerebellum, and the anterior cingulate and occipital areas was associated with a better response to 20 Hz rTMS. The opposite was true for a greater improvement after 1 HZ rTMS.

Limitations of the Current TMS Studies

Initial limitations such as the use of different coils, the number and duration of stimulation have now been overcome, but methodological parameters remain to be checked so that the indications for the use of rTMS are fully defined. These parameters include determining appropriate control stimulation and improving stimulus coil dispositions, increasing sample sizes in controlled and open-label studies, so that researchers can identify subgroups who would benefit from the treatment,[98] the restriction of heterogeneity between the sample under study (mental disorder, medication, heterogeneity in the administered medication), the use of double-blind study,[99] in order to limit the possibility of transmitting information from the evaluators to the participants about the nature of the treatment provided,[100] the determination of the duration of the response to MDD as well as the frequency and duration of maintenance treatments and the characteristics of patients who would benefit from maintenance treatment, the use of more structured clinical scales so that the results would be more accurate, the use of the same outcome definitions in terms of study results and interpretation of psychometric scales, as well as the use of the same psychometric scales, so that studies can be further evaluated among themselves.[101] Finally, in order to evaluate the effectiveness of rTMS, hospital readmissions, time of discharge from hospital and time of treatment should be considered.

Conclusion

The literature concerning rTMS and depression is very rich, but also heterogeneous in its objectives, in the populations included, and in stimulation settings. The methodology has improved significantly since 2000, with an optimisation of stimulation parameters (higher number of sessions and higher number of stimuli per session). A large amount of evidence supports the conclusion that HF rTMS of the left DLPFC and LF rTMS of the right DLPFC exerts an antidepressant effect, at least in the acute phase of an episode of unipolar depression. However, further studies are needed to investigate the efficacy of rTMS in bipolar depression. Another patient characteristic, which is not always well-specified in rTMS studies, is the question of drug-resistance. Most studies comprise depressed patients resistant to one or more psychopharmacological interventions. This is not only true for the oldest studies, but also for the most recent ones. In fact, the level of resistance, especially in terms of number of drug treatment failures at the time of the current episode, is highly variable between the studies and this may impact the response to rTMS therapy. A further crucial issue is the combination of pharmacological therapy with the application of rTMS. Some studies showed that the antidepressant effect of rTMS delivered to the DLPFC was probably an additive to the efficacy of antidepressant drugs and possibly potentiating, although not all studies demonstrate an add-on advantage from rTMS combined with antidepressants. These aspects need to be considered in the choice and development of therapeutic strategies and in determining the respective place of rTMS and drugs in the management of patients with depression.

Although rTMS appears to be undoubtedly efficacious for depression, the clinical relevance of its efficacy in daily practice is more questionable, as underlined by a recent meta-analysis.[102] The NICE guidelines information for the public December 2015 in the UK said: "Transcranial magnetic stimulation for depression is safe enough and works well enough for use in the NHS although benefits vary for different people "whilst NICE IPG 542 Dec 2015 states: "The evidence on repetitive transcranial magnetic stimulation for depression shows no major safety concerns. The evidence on its efficacy in the short-term is adequate, although the clinical response is variable. Repetitive transcranial magnetic stimulation for depression may be used with normal arrangements for clinical governance and audit."

Several methodological points should be defined as soon as possible to standardise and optimise the use of rTMS in the treatment of depression in routine clinical practice.[103] Since rTMS efficacy surely depends on the "dose" of stimulation (number of delivered pulses during a sequence of treatment), new rTMS protocols are being tested by intensifying the number of delivered pulses over shorter periods of time.[104,105] Other protocols propose to combine different rTMS paradigms according to priming strategies or to use stimulating coils other than the focal F8c, e.g., the H-coil, which delivers more widespread current into the depth of the brain. However, to improve rTMS therapy for depression in the future, the key aim will probably be to better define the protocol of maintenance. rTMS deserves a place in the standard toolbox of treatment resistance depression as it is effective and has a mild side effect profile.

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Ειδικό άρθρο

Η πρόοδος στον διακρανιακό μαγνητικό ερεθισμό (TMS) και οι εφαρμογές του στην ανθεκτική κατάθλιψη

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ΠΕΡΙΛΗΨΗ

Ο διακρανιακός μαγνητικός ερεθισμός (TMS) είναι μια μη επεμβατική μέθοδος διέγερσης του εγκεφάλου, η οποία λαμβάνει όλο και περισσότερη προσοχή, κερδίζοντας έδαφος για νέες κλινικές εφαρμογές. Μέσω παραγωγής ηλεκτρομαγνητικού πεδίου στον εγκεφαλικό φλοιό, η φλοιώδης δραστηριότητα μπορεί να ρυθμιστεί και να επιτευχθούν θεραπευτικά αποτελέσματα σε ποικίλες ψυχιατρικές και νευρολογικές διαταραχές. Σύμφωνα με τον Παγκόσμιο Οργανισμό Υγείας (WHO) η κατάθλιψη είναι η ασθένεια που προκαλεί τη μεγαλύτερη αναπηρία στον κόσμο και 350 εκατομμύρια άνθρωποι υποφέρουν από κατάθλιψη παγκοσμίως. Η μείζονα κατάθλιψη είναι η πιο κοινή διαταραχή που αντιμετωπίζεται με το TMS και η πρώτη ψυχική διαταραχή για την οποία το TMS έλαβε έγκριση από την Αμερικανική Αρχή Τροφίμων και Φαρμάκων (FDA). Στο παρόν άρθρο εισάγουμε τις βασικές αρχές του TMS, συζητάμε τα τελευταία δεδομένα που αφορούν την ασφάλεια χρήσης της μεθόδου και τις πιθανές παρενέργειες και παρουσιάζουμε διάφορα πρωτόκολλα θεραπείας καθώς και προγνωστικά απόκρισης στη μείζονα καταθλιπτική διαταραχή.

ΛΕΞΕΙΣ ΕΥΡΕΤΗΡΙΟΥ: Επαναληπτικός Διακρανιακός Μαγνητικός Ερεθισμός (rTMS), ραχιαίος-έξω προμετωπιαίος φλοιός, μείζονα καταθλιπτική διαταραχή, νοητικές νευροεπιστήμες, πρωτόκολλα rTMS.

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