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Transcranial magnetic stimulation

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Purpose of review

To present the state of the art of transcranial magnetic stimulation (TMS) therapy, especially when it is used in psychiatric disorders, on the basis of an exhaustive literature search from 2006 to date (June 2008) on TMS papers published in *Medline* and *Embase*. Other references and comments from our own experience started 8 years ago have also been taken into account.

Recent findings

The mechanism of action of TMS is now better understood. There is strong evidence of the safety and tolerability of TMS when standard protocols are used. The efficacy of the stimulation of the dorsolateral prefrontal cortex in depression is well documented, and there is evidence of the utility of TMS in posttraumatic stress disorder, in persistent auditory hallucinations in schizophrenia and in attention-deficit disorder with hyperactivity.

Summary

There is enough evidence of the efficacy and safety of TMS in depression to include this technique in the therapeutic protocols of major depression. However, more research is needed on the use of this technique in other psychiatric and nonpsychiatric disorders such as posttraumatic stress disorder, persistent auditory hallucinations, attention-deficit disorder with hyperactivity and tinnitus.

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Keywords

attention deficit disorder with hyperactivity, auditory hallucinations, dorsolateral prefrontal cortex, posttraumatic stress disorder, repeated transcranial magnetic stimulation, transcranial magnetic stimulation, treatment resistant depression

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Introduction

Transcranial magnetic stimulation (TMS) is only two decades old. Originally it was introduced to investigate in a noninvasive way the nervous propagation along the corticospinal tract, spinal roots and peripheral nerves in humans. The repeated transcranial magnetic stimulation (rTMS) was initially used as a therapeutic method in neuropsychiatry illnesses with abnormalities of the neuronal excitability [1]. Comprehensive and detailed information of the method appears in George and Belmaker's book [2••]. In 2007, TMS was approved for treatment-resistant depression in Canada, Australia, New Zealand, the European Union and Israel, whereas it is still in phase IV studies in the United States [3]. The rest of uses are still experimental.

TMS is safe and well tolerated with minimal side effects reported. Up to now there is no evidence neither of death nor epileptic seizures in published studies including over 10 000 treatment sessions. TMS is well tolerated with a low dropout rate for adverse events (4.5%) that were generally mild and limited to transient scalp discomfort or pain [4]. This high tolerability, along with the possible indications, facilitates its applicability.

The exact mechanism of action of TMS is still unknown. A recent study on cat visual cortex has shown that pulse trains of rTMS provoke a dose-dependent response, which is enhanced either with the duration or the intensity of stimulation [5•]. Short TMS pulse trains elicited an initial activation (approximately 1 min) and a prolonged suppression (5–10 min) of neural responses. Furthermore, TMS disrupted the temporal structure of activity by altering phase relationships between neural signals.

Neural activity changes were also reflected in haemodynamic signals; TMS led to an initial increase and subsequent longer lasting decrease in tissue oxygenation and haemoglobin concentration [6••]. In principle, dose-dependent linearity on this effect is confirmed in previous studies that obtained an increase in excitability in the dorsolateral prefrontal cortex (DLPFC) with high frequencies and transitory cortical inhibition with low frequencies [7]. On the contrary, there is evidence that rTMS has an effect in the tryptophan and serotonin

metabolism in limbic areas [8], whereas acute TMS application lacks the normalizing effect of BDNF that takes place with rTMS [9].

One of the aspects of major theoretical and practical consequences is the position of the coil. There are several standardized options for the manual placement of the coil, and an optically tracked frameless stereotaxic navigation procedure, similar to the one used in neurosurgery, is also available. Potential sources of imprecision are due to the fixation of a reference frame to the head of the patient and the referencing procedure according to certain landmarks. The accuracy in 1728 different sessions in nine patients (192 measurements for one patient) with the stereotaxic system of position of the coil has only 2.5 mm of mean deviation. This high stability makes the procedure very adequate for rTMS treatments [10]. Other systems to place the coil are the standard navigation systems, which reduce the errors due to the anatomical variability between individuals. In a case in which during the first week the system of anatomical approach was used and lead to a clinical improvement of the patient, during the second week the stimulation area was located using a navigation system in order to localize the BA 46 left, via MRI reconstruction was carried out, before and after the stimulation. It turned out that the place initially stimulated was the Broca's area, and that the DLPFC was not to 5 cm off the primary motor cortex of the hand but 8.3 cm. With the improvement of the localization, the efficacy of the treatment was improved when compared with the first week results [11]. The navigation systems allow more precision in the localization of the area to be stimulated than the standard visual anatomical system. Nevertheless, a recent study shows that the positioning of the coil by means of statistical visual approach is very consistent with the location by means of functional MRI (fMRI) [12]. In summary, although a maximum accuracy is desirable in the identification of the area to be stimulated, the classic visual anatomical systems are still a trustworthy resource.

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It is not possible to predict the position and the neuronal population to be stimulated by TMS in atrophic brains [13]. TMS in brains with atrophy requires identifying the target case by case. Factors such as the distance between scalp and the cortex must be taken into consideration when estimating the attenuation of the density of the flow.

Most of the clinical trials with TMS use a sham TMS as control, although patients seem to be able to feel differences in their sensations and from the noise and heat generated. Therefore, methods have been created in order to reproduce the subjective sensations in sham rTMS, both in fixed as well as mobile equipments [14]. A step further to also blind the researcher is a coil that electronically shifts form standard to the simulated application [15].

Transcranial magnetic stimulation in depression

TMS in psychiatry has been more widely used and investigated in depression. TMS has also been able to identify an asymmetry of the functioning of the brain hemispheres in depressive disorders. The reasons why in major depression (MDD) the right DLPFC (RDLPFC) is hyperactive and the left (LDLPFC) is hypoactive, remains poorly understood. Nevertheless, with fMRI, the hyperactivity of the RDLPFC correlates with the severity of the depression, which is also related to attention modulation. The hypoactivity of the LDLPFC is related to the presence of negative emotions [16].

All these aspects are highly important to choose the right technique of stimulation. In resistant depression, high-frequency rTMS (HFR-TMS) of the LDLPFC increases the activation of the left precuneus, whereas low-frequency rTMS (LFR-TMS) of the RDLPFC decreases the activity of the middle frontal gyrus. This reduction in the frontal activity does not seem to be unspecific, differing from the answer to the HFL-TMS [17]. On the contrary, rTMS of LDLPFC in healthy volunteers affects the modulations of regions involved in tryptophan and serotonin metabolism, in particular in the left parahippocampal gyrus (BA 28), the right insula (BA 13), right cingulate gyrus (BA 31) and the cuneus (BA 18) [8]. rTMS of LDLPFC is able to normalize serum concentrations of BDNF, often reduced in patients with major depression, in spite of the fact that acute TMS in healthy volunteers does not alter the levels of BDNF [9].

Ten Hertz rTMS on the LDLPFC has a higher efficacy than sham rTMS [18]. rTMS exerts antidepressant effects either by enhancing left DLPFC excitability with 10 Hz rTMS or by decreasing right DLPFC excitability with 1 Hz rTMS [19••]. The different mechanism of action for the high (increased excitability) and low (transitory inhibition or dysfacilitation) frequencies had been described previously by Pascual-Leone [7].

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Several controlled and open studies show high levels of safety of rTMS [4,20]. Treatment discontinuation because of side effects is only 4.5%. There have been no deaths nor epileptic seizures reported in more than 10 000 treatment sessions in published studies. The side effects are minimal and well tolerated, consisting principally of migraines and minor skin injuries in the application area. There are no verified auditory or cognitive deficits after rTMS.

This safety allows an extension of treatment in resistant depression, suggesting that longer courses of treatment may have additional therapeutic benefit, that is, 10 Hz rTMS on LDLPFC. In a randomized study comparing active and sham rTMS in treatment-resistant major

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depressive patients who failed to respond to 4-week treatment period, 26% of them showed good response and 11% full remission after a 6-week treatment period [21].

The safety of the treatment encourages the application in neurological illnesses with depressive comorbidity that may deteriorate with the use of antidepressants and even more with electroconvulsive treatment (ECT). Ten Hertz rTMS of LDLPFC has been useful in the treatment of Parkinson's disease, not only for depressive symptoms but also for anxiety and motor symptoms, especially during the 'off' moments [22].

rTMSs has also been used as an augmentation strategy in resistant depressions. Good result have been published in a real vs. sham 10 Hz rTMS of LDLPFC randomized study when 20 mg/day of escitalopram was added in patients with severe depression who failed to respond to two previous nontricyclic antidepressant treatments [23]. Such results obtained are similar to those with other pharmacological augmentation strategies, and therefore, rTMS must be considered in the therapeutic protocols prior to ECT [24•].

For the moment, no strong predictors of good response have been identified [25], probably because of the heterogeneity of the samples and the design and sample size of the studies [26]. Nevertheless, in a revision of rTMS of LDLPFC [27], it seemed that younger age and less resistance to treatments were better predictors of a good response.

Transcranial magnetic stimulation in schizophrenia

A reduced cortical inhibition has been described as a characteristic of schizophrenia [2••], which has been attributed to a GABAergic deficit [28]. Furthermore, connectivity abnormalities between modules for motor control, sensory–motor synchronization, temporary perception and conscience of the action, are present in schizophrenia and could be, at least theoretically, interrupted by rTMS [29].

On the contrary, deficits in backward masking (the perception of a briefly displayed visual stimulus target is impaired when followed by another visual stimulus task presented in the same location) have been reported in schizophrenia. TMS has been used to identify a subgroup of patients having impaired evaluation of visual stimuli. TMS data also suggest that this deficit may not be localized to the occipital cortex [30]. Negative symptoms do not seem to respond to bilateral prefrontal cortex (PFC) rTMS, and only a tendency was appreciated in the improvement in the autistic symptoms after 3 weeks of TMS treatment session [31].

What seems to be more interesting is that rTMS turns out to be an effective intervention for the auditory hallucinations of the schizophrenia. A meta-analysis including ten studies and 212 patients conclude that 1 Hz rTMS of temporoparietal cortex has an influence in the neurobiology of auditory hallucinations without having an effect on the general psychotic symptoms [32]. The treatments for the auditory hallucinations of the schizophrenia have only been provided for short periods of time, although in two cases of relapsing the treatment was successfully reused [33], but this was not the case in another publication [34].

Transcranial magnetic stimulation in other psychiatric disorders

The efficacy of rTMS of RDLPFC in PTSD has been reported [35], and more evidence on the combination of 1 Hz rTMS and exposure therapy [36], being specially effective on hyperarousal symptoms. TMS application can be of interest along with augmentation of exposure with drugs such as propranolol [37]. AQ6

In obsessive–compulsive disorder (OCD), the results are contradictory. Two double-blind placebo-controlled studies comparing rTMS and sham rTMS have shown that TMS is ineffective in OCD, one of them in combination with SSRI [38,39]. The problem here is to identify the target and the strategy (10 Hz stimulation vs. 1 Hz inhibition). The other problem may be the heterogeneity of samples. AQ7

In adults with attention-deficit disorder with hyperactivity (ADDH), TMS of double pulse detects a decrease in the inhibitory motor region similar to the one found in children with ADDH [40]. TMS may be used as a diagnostic tool to establish disturbed impulsivity and hyperactivity on a neurophysiological level.

Transcranial magnetic stimulation for non psychiatric uses

In addition to the psychiatric uses previously commented, TMS can be used in other applications of neuroscience.

Neuroanatomy of the continuum between child and adult attention-deficit disorder with hyperactivity

TMS has been used to measure changes in cortical excitability induced by drugs [41]. TMS may have a place in the study of the epilepsy and possibly in the treatment of some concrete types. We have already mentioned the therapeutic possibilities in movement disorders [2••]. Furthermore, TMS can facilitate the study of the spastic diplegia in children by detecting alterations in cortical inhibitory functions [42].

The possible uses in paediatric populations are attractive, taking into account possible neurotrophic effects that could counteract the trend to chronicity of many disorders of childhood. The safety profile of rTMS is also to be considered in neuropaediatrics, as more than 1000 children have been treated with rTMS in 84 studies and all of them do not have any important side effects [43••].

Other uses of transcranial magnetic stimulation

rTMS has a therapeutic utility in pain, although for a limited duration. In a 10 Hz rTMS of LDLPFC, with sham rTMS in depressed patients, a reduction in pain in the muscles and bones, not related to antidepressant effects, was shown. This raises the possible implication of motivational factors in evaluating pain perception stimuli [44].

rTMS is useful for the treatment of tinnitus due to abnormal focal brain activity. Five sessions of low-frequency rTMS of the left auditory cortex in healthy volunteers resulted in a significant extension of the cortical silent period, producing an increase in the subcortical inhibition [45].

Conclusion

rTMS is a relatively new method with important efficacy and safety profile. rTMS has clinical applications in psychiatry, specially in the treatment of resistant depression. rTMS should probably be introduced in the therapeutic protocols of treatment-resistant cases along with other augmentation strategies and before considering ECT.

AQ8 TMS and rTMS provides novel insights in the diagnosis and treatment of other disorders such as ADDH, schizophrenia (specially in the treatment of auditory hallucinations) and PTSD, and can be useful in depression comorbid with diseases were it is not recommended the use of antidepressants.

rTMS is a sure method, with no serious side effects when used according to the established protocols. The possible side effects are usually minimal and well tolerated, similar in frequency to those obtained with sham rTMS.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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