

REVIEW ARTICLE

Repetitive transcranial magnetic stimulation (rTMS) in the treatment of depressive disorder

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Abstract

This article deals with the use of repetitive transcranial magnetic stimulation (rTMS) in the treatment of depressive disorder. The method involves influencing the brain using variable magnetic field. Repetitive TMS is safe, well-tolerated and has very few adverse effects. It is the treatment of depressive disorder where psychiatrists have most experience with this method which, however, is starting to be used for the therapy of other mental disorders as well. Repetitive transcranial magnetic stimulation has been proven to influence cortical excitability and the metabolic activity of neurons. Many studies of its effectiveness in the treatment of depressive disorder have been performed to date and can be divided into three generations. The results of different studies have been summarised in several meta-analyses; the most recent ones in particular show that rTMS constitutes a promising therapeutic method, although a number of questions concerning mainly the exact mechanism of its action, the setting of the most appropriate stimulation parameters and the selection of the most susceptible patients remain unanswered.

Abbreviations:

ACTH – adrenocorticotrophic hormone, CI – confidence interval, CRF – corticoreleasing factor, DLPFC – dorsolateral prefrontal cortex, ECT – electroconvulsive therapy, EEG – electroencefalography, ES – effect size, HRSD – Hamilton rating scale for depression, Hz – Hertz, MADRS – Montgomery and Asberg depression rating scale, NNT – number needed to treat, OCD – obsessive compulsive disorder, rTMS - repetitive transcranial magnetic stimulation, SSRI – selective serotonin reuptake inhibitors, TMS – transcranial magnetic stimulation, TSH – thyroid stimulating hormone

INTRODUCTION

Transcranial magnetic stimulation (TMS) represents a relatively new method used in neurophysiological research in which it helps to measure various cortical phenomena, including cortical inhibition and plasticity (Prikryl *et al* 2009), but also in the diagnosis and treatment of certain neuropsychiatric disorders.

TMS PRINCIPLE AND HISTORY

The principle of this method is based on Faraday's law of electromagnetic induction formulated in 1831. This law states that around the primary coil through which a time-varying current is flowing, a changing magnetic field is created which is able to induce a secondary current in conductors found within its reach. The

patient's brain, too, may be one of such conductors. The secondary current induced is, according to Lenz's law, in the direction opposing the primary current (Daskalakis *et al* 2008).

Scientists examined the possibilities of non-invasive and focal stimulation of the brain using magnetic field as early as at the turn of the 19th and 20th century. D'Arsonval in 1896 and Thomson in 1910 built large electromagnetic stimulators which, however, could not produce a magnetic field of sufficient intensity to be able to influence brain tissue, so for example D'Arsonval succeeded only in inducing "phosphenes" (i.e. perceived flashes of light) by stimulating the retina (Burt *et al* 2002).

It was not until 1985 that Barker and his collaborators developed a device that could generate a magnetic field of sufficient intensity to depolarise cortical neurons. This device consisted of a stimulation coil connected to a capacitor capable of generating a sufficiently large electrical current over a very short time interval, this principle forming the basis of all modern devices (Barker 1991). The discharging of the capacitor makes this current flow through the stimulation coil, generating a changing magnetic field that lasts approximately 100–300 milliseconds and its intensity ranges from 1 to 2.5 Tesla – an intensity comparable with that of magnetic resonance scanners and about 20 000 to 50 000 times larger than the magnetic field of the Earth. This magnetic field then passes without resistance through the soft tissues of the head and the skull and induces a secondary electrical current in the brain, resulting in the depolarisation of neurons (Post & Keck 2001).

THE TMS PROCEDURE AND ITS PARAMETERS

During the stimulation, an insulated metal coil is placed over the patient's head and delivers a changing electrical current producing a changing magnetic field perpendicular to the current passing through the coil. As has been mentioned above, this magnetic field passes without resistance through the soft tissues of the head and the skull to reach the conductive brain tissue in which it induces a secondary electrical current parallel to the primary current, but, according to the abovementioned Lenz's law, in the opposite direction (Burt *et al* 2002).

Magnetic pulses may be administered individually or in pairs that are a few milliseconds apart (so-called paired-pulse stimulation), or repeatedly in a sequence, or "train", lasting from seconds to minutes (the so-called repetitive transcranial magnetic stimulation, rTMS). The first two options are used primarily for research and diagnostic purposes; rTMS is used mainly in the treatment of certain neuropsychiatric disorders.

Repetitive transcranial magnetic stimulation is defined by the number of pulses per second, or frequency in Hertz (Hz). According to the frequency it is then divided into "low-frequency" („slow“) rTMS with 1 Hz or less and "high-frequency" ("fast") rTMS with

more than 1 Hz (usually between 5 and 25 Hz). Another parameter of stimulation is its intensity expressed as the percentage of individual resting motor threshold. Motor threshold is defined as the minimal intensity of the stimulus able to produce muscle contraction (usually in one of the small muscles of the hand, e.g. the abductor pollicis brevis) when applied on the motor cortex, in at least five in ten successive trials. The most commonly used stimulation intensity then varies between 80 and 120% of individual resting motor threshold. Other stimulation parameters include the length of the train of pulses and also the duration of the pause between them ("intertrain"), the total number of pulses administered during one session, the total number of individual sessions, the stimulation coil localisation, the type of coil (the most commonly used type in rTMS is the so-called figure-of-eight coil; then there are oval-shaped coils, conical coils etc.) and its position and orientation with respect to the patient's head (Burt *et al* 2002).

INDICATIONS OF rTMS IN PSYCHIATRY

Most experience with the use of rTMS in the treatment of mental disorders has been associated with depressive disorder, as will be mentioned below; the method is also used – still mainly experimentally – to treat schizophrenia, which concerns specifically low-frequency rTMS targeting the temporo-parietal cortex area in patients suffering from resistant auditory hallucinations and high-frequency rTMS targeting the prefrontal cortex area in patients with dominant negative symptoms (Fitzgerald & Daskalakis 2008). The findings concerning the effectiveness of rTMS in patients with auditory hallucinations are summarised in a meta-analysis by Aleman *et al.* from 2007 which included ten studies and proved a significant reduction in the severity of auditory hallucinations using active stimulation in comparison with sham (inactive) stimulation. Findings on the effectiveness of rTMS in patients with negative symptoms are summarised in a meta-analysis by Dlačáček-de Lange *et al.* from 2010 which included a total of nine studies and also proved that rTMS may be, in this indication as well, an effective therapeutic method, particularly using a frequency of 10 Hz and a treatment duration of at least three weeks. According to the third meta-analysis, however, this is not quite clear (Aleman *et al* 2007; Dlačáček-de Lange *et al* 2010; Freitas *et al* 2009).

Repetitive TMS is also being tried in the treatment of mania, namely the high-frequency stimulation of the right prefrontal cortex. There is, however, less experience in this indication than in the previous ones (Grisaru *et al* 2008).

Other experimental indications include the treatment of obsessive-compulsive disorder (OCD). The first data about the use of rTMS, namely for the stimulation of the prefrontal cortex, appeared to be quite promising; nevertheless, other studies, this time double-blind, placebo-controlled, did rather not confirm them, with

the exception of a study by Mantovani *et al.*, who, however, used a different target of stimulation – the area of the supplementary motor cortex (Greenberg *et al* 1997; Sachdev *et al* 2001; Alonso *et al* 2001; Mantovani *et al* 2006; Sachdev *et al* 2007; Prasko *et al* 2006). Besides the abovementioned indications there have also been attempts to use rTMS for instance in the treatment of post-traumatic stress disorder, panic disorder and even mental bulimia (Greenberg & Lisanby 2008; Walpoth *et al* 2008). Transcranial magnetic stimulation was also recently tried in a pilot study in patients with ADHD (Bloch *et al* 2010).

Last year, Slotema and colleagues processed the results of studies using rTMS in the treatment of depressive disorder, auditory hallucinations, negative symptoms of schizophrenia and OCD. They concluded that in terms of effectiveness, rTMS is suitable for the treatment of depressive disorder, auditory hallucinations and probably the negative symptoms, but not OCD (Slotema *et al* 2010).

CONTRAINDICATIONS AND ADVERSE EFFECTS OF rTMS

Repetitive transcranial magnetic stimulation is a safe and well-tolerated method of treatment, which is true even for its administration twice a day and even for the so-called accelerated rTMS when fifteen sessions were administered in the course of merely two days (Loo *et al* 2007; Holtzheimer *et al* 2010). Absolute contraindications of high-frequency rTMS include an epileptic history and elevated risk of an induction of epileptic paroxysm, such as intracranial hypertension, use of drugs that may lower seizure threshold, history of brain ischemia or a pathological EEG recording. On the contrary, the use of low-frequency stimulation for the treatment of epilepsy is being tried (Santiago-Rodríguez *et al* 2008). Other absolute contraindications of both high and low-frequency rTMS include a metal implant in the cranium, except for the mouth, and also an implanted pacemaker or a drug pump. Relative contraindications include pregnancy, although it is not known that rTMS could endanger its course in any way (Rau *et al* 2007). The most serious adverse effect of rTMS is the induction of an epileptic paroxysm even in an individual without predispositions. This risk, however, is very low; its value is usually indicated as approximately one case in a thousand or less (Příkryl & Kučerová 2005). Only slightly more than ten cases have been described in the world altogether. Such a seizure occurs during or shortly after the stimulation and does not pose the risk of epilepsy developing. Other adverse effects include pain at the stimulation site during application, which, according to the literature, occurs in 10–30% of patients. But the pain is usually mild, transient and only very rarely leads to an early termination of treatment. Occasionally, headaches may occur after stimulation, but they are usually mild and transient,

too, and respond to common analgesics (Rau *et al* 2007). A temporary elevation of hearing threshold was also described in several patients; however, an average change of hearing threshold did not occur in the studied cohort. Similarly, no changes in the EEG recording and neuropsychological performance were found (Loo *et al* 2001). As for mental adverse effects, they are also extremely rare. In a few patients suffering from bipolar affective disorder a shift into mania was described after stimulation for a depressive episode; in one case the development of psychotic symptoms occurred after rTMS (Ella *et al* 2002; Zwanzger *et al* 2002).

REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (rTMS) IN THE TREATMENT OF DEPRESSIVE DISORDER

Transcranial magnetic stimulation started to be regarded as a potential method of treatment of depressive disorder after the influence of TMS on mood was found out (Bickford *et al* 1987). Stimulation of the vertex was tried in the beginning, but following inconsistent results and successful stimulation of the left dorsolateral prefrontal cortex (DLPFC), most studies have focused on this particular area. The stimulation site is usually defined as the location 5 cm rostral to the area of the motor cortex the stimulation of which determined the resting motor threshold. Besides the stimulation of the left DLPFC, rTMS of the same area in the opposite hemisphere is also being successfully tried, namely of the right DLPFC (Klein *et al* 1999; Fitzgerald *et al* 2003). According to the recent works, however, the “5-cm method” of coil targeting is inaccurate and it is more suitable to use neuronavigation or at least the “10–20 method” used in EEG, with the site for stimulation of the left DLPFC being found between the F3 and F5 electrodes, closer to the F5 electrode (Schönfeldt-Lecuona *et al* 2010; Rusjan *et al* 2010).

Mechanism of antidepressant action of rTMS in animal models

The mechanism of antidepressant effect is not quite clearly elucidated. It was found in animal models using the swim test that rTMS leads to similar effects as ECT, and these are connected with variation in the dopamine level, which could mean that rTMS also affects dopaminergic transmission, particularly in the hippocampus and the nucleus accumbens (Post & Keck 2001). It is also being shown that rTMS normalises the function of the hypothalamic-pituitary-adrenal axis and, similarly to antidepressants, reduces CRF, ACTH and corticosterone outputs (Czeh *et al* 2002; Keck *et al* 2000, 2001). Changes in neurotransmitter levels were also studied in animal models. Besides the abovementioned increased release of dopamine, an influence on serotonergic and noradrenergic systems was also observed, but the results of the studies are inconsistent (Post & Keck 2001). Nevertheless, it can be said that as far as

the impact on the levels of other neurotransmitters is concerned, the effect of rTMS is similar to that of ECT (Loo 2008). A few studies in animal models also demonstrated a neuroprotective effect. For instance, Müller et al. recorded an elevation in the level of BDNF in the gyrus dentatus and other areas of the hippocampus in 2000 (Müller *et al* 2000), Post and colleagues described a neuroprotective effect of rTMS against oxidative stress in 1999 (Post *et al* 1999) and Funamizu et al. observed a reduced effect of neurotoxins on nigrostriatal neurons in rats in 2005 (Funamizu *et al* 2005). The existing results thus point at the possibility of a neuroprotective effect of rTMS, resembling that of antidepressants and ECT, although the effect of stimulation on neurogenesis is not clear yet (Loo 2008). There are also data from several studies which indicate that rTMS may, using specific stimulation parameters, induce persisting changes in the functioning of neurons that are similar to the changes induced by anticonvulsants used as mood stabilisers or by electroconvulsive therapy (Loo 2008).

Mechanism of antidepressant action of rTMS in clinical studies

Most clinical studies examining the antidepressant effects of rTMS are based on the use of neuroimaging methods that focus on changes in blood flow through the brain, changes in the metabolism of neurons and also on changes in the activity of neurons; effects of stimulation on the endocrine system are also examined.

In 1999, Kimbrell and colleagues noted that global hypometabolism was related to the response to high-frequency rTMS and also found a tendency to improvement after low-frequency rTMS in the case of global hypermetabolism prior to stimulation (Kimbrell *et al* 1999). A year later, Speer also noted in depressive patients after stimulation with 1-Hz frequency, a decrease in perfusion in certain areas of the brain, while after stimulation with 20-Hz frequency he noted an increase in perfusion at the stimulation site and also in limbic and paralimbic regions (Speer *et al* 2000). Baeken described the correlation between the positive response to high-frequency stimulation and the metabolic changes in parts of the anterior cingulum (Brodmann's areas 24 and 32) (Baeken *et al* 2009). Li, on the basis of the results of his own study, suggests that the antidepressant mechanism of add-on rTMS therapy may be reflected by the suppression of hyperactivity in the left temporal cortex and the fusiform gyrus and perhaps through enhancing the function of the medial prefrontal cortex and anterior cingulum (Li *et al* 2010).

As for the activation of neurons, it has been proven that high-frequency stimulation increases cortical excitability (Fitzgerald *et al* 2006), whereas low-frequency stimulation may decrease it, which was demonstrated e.g. by Chen and colleagues in 1997 (Chen *et al* 1997). Neurophysiological effect of rTMS of various frequencies has also been studied recently, namely of 1 Hz, priming (6 Hz followed by 1 Hz), 10 Hz and 20 Hz on

cortical inhibition in healthy subjects. For higher frequencies, this study demonstrated a more pronounced extension of inhibition mechanisms linked to GABA-B receptor-mediated neurotransmission, which corresponds to findings that GABAergic neurotransmission tends to be disrupted in patients with depression and is enhanced using ECT or SSRI (Daskalakis *et al* 2006; Daskalakis *et al* 2008). There are presumptions that rTMS does not simply cause normalisation of prefrontal hypoactivity and that high-frequency stimulation increases and low-frequency stimulation decreases cortical activity, but that through the connection from the prefrontal cortex also the more remote limbic and paralimbic regions are influenced. Nevertheless, further studies are needed that would clarify which other areas of the brain and in what way are involved in the antidepressant effect of rTMS (Loo in Wassermann *et al* 2008).

As for the effects of rTMS on the neuroendocrine system, an elevation of thyroid stimulating hormone (TSH) was found (George *et al* 1996; Cohrs *et al* 2001; Szuba *et al* 2001) as well as normalisation of the dexamethasone suppression test in correlation with mood improvement following rTMS (Pridmore 1999; Zwanzger *et al* 2003), whereas changes in progesterone levels and dehydroepiandrosterone were not found in another study (Padberg *et al* 2002). On the whole, it can be said that it is not possible so far to explain the antidepressant effect of rTMS on the basis of studies performed to date examining hormonal changes after stimulation (Loo 2008).

Studies and meta-analyses dealing with rTMS in the treatment of depressive disorder

Dozens of studies dealing with the effectiveness of rTMS in the treatment of resistant depression and at least nine meta-analyses summarising the results of individual studies (conducted not only in patients suffering from resistant depression) have been published to date. Daskalakis divides these studies into three generations: the first generation includes older studies that examined the effectiveness of rTMS using a maximum of ten sessions, his second generation contains studies with more than ten sessions and the third generation covers studies that make use of certain newer procedures, e.g. bilateral rTMS (other stimulation parameters as well as design in individual studies differ) (Daskalakis *et al* 2008).

1st generation studies

The first positive results of the use of high-frequency stimulation of the left prefrontal cortex were noted in an open-label study by George and colleagues in 1995 in six patients with resistant depression (George *et al* 1995). A year later, similarly promising results were also published by Pascual-Leone and colleagues who examined seventeen patients suffering from resistant depression with psychotic symptoms. In this case it was

a cross-over, randomised and placebo-controlled study with sham rTMS and stimulation of different cortical areas as a control lasting always one week (Pascual-Leone *et al* 1996). Other studies by George and colleagues from 1997 and Figiel and colleagues from 1998 also recorded a significant improvement in patients with depression after two weeks of active stimulation in comparison with sham (George *et al* 1997; Figiel *et al* 1998).

Several studies also dealt with low-frequency rTMS of the right prefrontal cortex. A major study by Klein and colleagues from 1999 in seventy patients randomized either into the active arm or the sham arm under the conditions of a double-blind study may serve as an example. After two weeks of study treatment, 49% of patients from the active arm were assessed as responders, compared with 25% of patients from the sham arm (Klein *et al* 1999). Similarly positive results were obtained in the studies by Geller and colleagues in 1997, Feinsod and colleagues a year later and Menkes and colleagues in 1999 (Geller *et al* 1997; Feinsod *et al* 1998; Menkes *et al* 1999). Not all studies, however, scored such success. Loo and colleagues, for instance, in her study from 1999, found no significant difference between active and sham high-frequency stimulation of the left prefrontal cortex administered for two weeks, and Berman and colleagues in 2000 found only a slight reduction in the severity of depressive symptoms following the ten-day high-frequency stimulation of the same area, and also a number of other studies had a similar outcome (Loo *et al* 1999; Berman *et al* 2000). Daskalakis attributes these results to several reasons. Firstly, to the fact that the majority of patients in these studies were resistant, so in at least some of them a comorbidity could have been present which negatively influenced the result; secondly, to the fact that stimulation parameters (frequency, intensity, duration) varied among the studies; thirdly, to the fact that the results could have been also influenced by concomitant medication used in these studies; and finally, fourthly, to the absence of a consistent and accurate method to determine the site of stimulation (Daskalakis *et al* 2008).

2nd generation studies

Increasing the number of sessions from ten, a number common initially, is logical if we compare the effectiveness of two-week ECT which is very often insufficient, especially in resistant depressions, with ECT extended to five weeks (Daskalakis *et al* 2008). One of such studies was also a study by Fitzgerald and colleagues from 2003 in which sixty patients with resistant depression were divided into three groups. In one of them the patients were treated with active high-frequency rTMS, in the second one with low-frequency rTMS and in the third one they underwent sham stimulation. During the study, a continuous improvement of the patients' condition in both active arms was observed (Fitzgerald *et al* 2003). In another study, Avery and colleagues compared a group of patients with resistant depression

treated by high-frequency rTMS with a control sham group. In a three weeks' time he noted a response in 30.6% of patients in the active arm and a remission in 20% of patients, compared to 6.1% and 3% in the control group (Avery *et al* 2006).

3rd generation studies

Bilateral rTMS appears to be a promising method with regard to the fact that the superiority of bilateral ECT over unilateral has been proven and also the fact that high-frequency rTMS of the left DLPFC as well as low-frequency rTMS of the right DLPFC is effective. Only a few attempts using bilateral stimulation have been made so far. The first attempt at simultaneous bilateral stimulation was not successful (Loo *et al* 2003). Then there were trials of sequential bilateral stimulation, but this was either in a small cohort of seven patients (Cohen *et al* 2003) or for a short period of time lasting only five days (Conca *et al* 2002). Other studies did not demonstrate a statistically significant difference between bilateral stimulation and the common unilateral high-frequency rTMS either (Hausmann *et al* 2004; Rybak *et al* 2005). According to Daskalakis, this happened for two main reasons. Firstly, bilateral rTMS was not compared with unilateral and sham in sufficiently large cohorts and secondly, the duration of these studies did not exceed ten days (Daskalakis *et al* 2008). Fitzgerald and colleagues in 2006 compared sequential bilateral rTMS with sham rTMS in a total of fifty patients for six weeks, which is a longer period than in the preceding cases. At the end of the study, more than 50% of patients reached a response and 36% of patients reached a remission in the active arm, compared to less than 10% and no patient in the control arm. As for patients in the sham arm who were transferred to bilateral stimulation after the study ended, a further 45% reached a response and 33% remission (Fitzgerald *et al* 2006). Nevertheless, in another study by Fitzgerald comparing unilateral right-sided stimulation with two forms of bilateral rTMS (right-sided low-frequency followed by left-sided high-frequency, and low-frequency applied on both hemispheres) no substantial difference between the individual forms of stimulation was found (Fitzgerald *et al* 2010). And, in a study by Pallanti, unilateral low-frequency stimulation was even found to be more effective than bilateral rTMS (right-sided low-frequency followed by left-sided high-frequency) (Pallanti *et al* 2010). On the other hand, the set-up of stimulation parameters in a prospective, multicenter, randomised, active sham stimulation-controlled study by George and colleagues proved good; this study used the intensity of 120% of motor threshold and a total of 3,000 pulses during each session; there were fifteen sessions followed by another fifteen in patients who improved (George *et al* 2010).

Meta-analyses

The effectiveness of rTMS in the treatment of depression can be best testified to by meta-analyses, in which

the results from individual studies are statistically processed.

One of the first meta-analyses was performed by McNamara and colleagues in 2001. Out of sixteen studies under consideration that had been published until then, he excluded eight because they lacked a randomised control group and one since a group of patients treated with ECT was used as a control group. In the seven remaining studies, high-frequency rTMS of the left hemisphere was applied in five cases, low-frequency rTMS of the right hemisphere in one case and high as well as low-frequency stimulation in the last one. The conclusion of this meta-analysis was that rTMS is effective in the treatment of depressive disorder (McNamara *et al* 2001).

Another meta-analysis was published by Holtzheimer and colleagues in the same year. It included twelve studies (eleven of them using stimulation of the left DLPFC) whose weighted mean effect size was 0.81 (95% CI: 0.42, 1.20, $P < 0.001$), but the number of responders (those who achieved at least a 50% reduction in the severity of depressive symptoms on the HRSD scale) was low (13.7% compared to 7.9% in control sham groups). The authors therefore concluded that active rTMS is statistically more effective than sham stimulation in the treatment of depression (with medium to large effect size), but the clinical effect is only mild (Holtzheimer *et al* 2001).

A year later, Burt and colleagues performed another meta-analysis, dividing the studies included into three categories. The first one contained nine open-label and uncontrolled studies, in the second one there were 23 studies controlled by sham stimulation or eventually otherwise, and, finally, the third one comprised three studies comparing rTMS with ECT. In the case of the open-label studies he found a statistically significant change with weighted effect size (Cohen's d) of 1.37, which corresponds to large statistical effect. Nonetheless, the clinical effect was relatively mild – on average there was a reduction in the severity of depressive symptoms assessed on the HRSD or MADRS scale of 37.03%. In the case of the controlled studies the effect size (Cohen's d) was 0.67 which, according to the authors, corresponded to medium-large statistical effect, whereas the clinical effect was again assessed as a rather mild one (reduction in the severity of depressive symptoms by 23.82% compared to 7.30% in control groups). A meta-analysis of ECT-controlled studies demonstrated a greater effect of ECT, although the difference in the percentage improvement was only small (54.47% compared to 47.13%) and in the case of rTMS it was higher than in the studies from the first two categories, which, according to the authors, was given by a longer duration of treatment than the usual one or two weeks (Burt *et al* 2002).

In the same year, Kozel and George came up with another meta-analysis. They included in it a total of twelve randomised, sham stimulation-controlled stud-

ies of the left prefrontal cortex with 230 subjects. The cumulative effect size found was 0.53; the authors concluded that their meta-analysis supports the hypothesis that rTMS of the left prefrontal cortex represents a method of choice for acute antidepressant treatment with a statistically significant effect size and measurable clinical improvement (Kozel & George 2002).

In 2003, Martin and colleagues published in the Cochrane database a meta-analysis which was rather critical of the use of rTMS in the treatment of depression. He included into it a total of fourteen randomised studies that compared rTMS with sham stimulation. After two weeks of treatment a statistically significant improvement after active rTMS was proved, which, however, was not significant any more after a two-week follow-up. Martin assessed the quality of these studies as generally low, arguing that they do not prove the effectiveness of rTMS in the treatment of depression (Martin *et al* 2003).

Two years later, another meta-analysis was elaborated by Couturier. The inclusion criteria were relatively strict and comprised, *inter alia*, also the duration of rTMS of only five to ten days. Out of nineteen studies under consideration, therefore, only six of them were included in the meta-analysis with a total number of 91 subjects. The author did not prove a statistically significantly greater effectiveness of active rTMS in comparison with sham stimulation in this meta-analysis (Couturier 2005). A weak point of this meta-analysis, however, is usually seen in the fact that due to the low number of studies and subjects included, its power to find a significant difference between active and sham stimulation is very limited (Daskalakis *et al* 2008).

In 2007, Gross and colleagues tried to find out whether recent studies using new parameters of stimulation have larger clinical effect. They compared a total of five studies with 274 patients with older studies that Martin had included in his meta-analysis and that included 324 patients. The resulting pooled effect size (standardised mean difference) of the more recent studies was -0.76 , and that of the older studies -0.35 , which is markedly lower. According to the authors of this meta-analysis it was thus confirmed that the more recent studies prove a greater antidepressant effect of rTMS, primarily thanks to improved stimulation parameters and the inclusion of a higher number of patients (Gross *et al* 2007).

A year later, two meta-analyses were published. Into the first of them, which did not appear in print until 2009, Schutter included a total of thirty double-blind, sham stimulation-controlled parallel-group studies with 1164 patients examining the antidepressant effect of high-frequency rTMS applied on the area of the left DLPFC. A weighted mean effect size amounting to 0.39 was found, which was assessed as robust and comparable with common antidepressants (Schutter 2009).

The second meta-analysis from 2008 by Lam and colleagues included 24 randomised, sham stimulation-

controlled studies in altogether 1092 patients with resistant depression (i.e. those who had failed at least one treatment trial). The meta-analysis proved that active rTMS was significantly more effective in comparison with sham rTMS (the response was achieved in 25% of patients in comparison with 9% and remission in 17% of patients treated with active rTMS compared to 6% treated with sham rTMS). According to the authors of this meta-analysis, rTMS is effective in the therapy of resistant depression, but further studies need to be carried out before it can be regarded as the method of first choice in this indication (Lam *et al* 2008) (for overview of the meta-analyses, *see Tab. 1*).

Prediction of effectiveness and duration of the antidepressant effect of rTMS

In an effort to select patients suitable for treatment with rTMS, some researchers dealt with the predictors

of effectiveness of this treatment method. These predictors can be divided into patient-related factors and treatment-related factors (Lisanby *et al* 2009). The first group contains the duration of the current depressive episode, pharmacoresistance and age. Fregni and colleagues described that younger patients and patients less resistant to treatment achieved better results after the therapy using rTMS (Fregni *et al* 2006). Also Brake-meier and colleagues stated that patients least resistant to treatment as well as patients with shorter duration of the current episode showed greatest improvement after rTMS. He also found out that patients with sleep disturbances derived greater benefit from the treatment (Brakemeier *et al* 2007). In a recent study, Lisanby and colleagues demonstrated in a cohort of altogether 301 patients that the strongest predictor of a positive effect of rTMS is a low number of prior failed treatment trials in the course of the current depressive episode,

Tab. 1. Overview of meta-analyses of rTMS effectiveness in the treatment of depressive disorder.

Meta-analysis (authors, year of publication)	Studies included	Results	Evaluation of rTMS effectiveness
McNamara <i>et al</i> 2001	5 studies with 81 subjects	NNT 2,3 (95% CI 1.6-4.0)	Effective
Holtzheimer <i>et al</i> 2002	12 studies using rTMS of left or right DLPFC	Weighted mean ES 0.81 (95% CI 0.42-1.20, p<0.001) 13.6% responders vs. 7.9%	Rather effective
Burt <i>et al</i> 2002	Open-label studies (9) Controlled studies (23) Studies comparing ECT and rTMS (3)	Cohen's d=1.37 (reduction in the severity of symptoms by 37.03%) Cohen's d=0.67 (reduction in the severity of symptoms by 23.82% vs. 7.30%) Cohen's d=0.21 (reduction of 54.47% vs. 47.13% in favour of ECT)	Rather effective
Kozel & George 2002	12 studies with 230 subjects using left-sided rTMS	Cumulative ES 0.53	Effective
Martin <i>et al</i> 2003	14 studies (13 of them using left-sided high-frequency rTMS) with 324 subjects	Standardised mean difference -0.35; (95% CI -0.66 to -0.04) After 2 weeks standardised mean difference -0.33; (95% CI -0.84 to 0.17)	Rather ineffective
Couturier 2005	6 out of 19 studies with high-frequency rTMS of left DLPFC with 91 subjects	Weighted mean difference -1.1 (95% CI -4.5 to 2.3)	Ineffective
Gross <i>et al</i> 2007	5 recent studies with 274 subjects compared with older studies from Martin's meta-analysis with 324 subjects	Standardised mean difference of recent studies -0.76 (95% CI -1.01 to -0.51)	Effective
Schutter 2009	30 studies with 1,164 subjects using high-frequency rTMS of left DLPFC	Weighted mean ES 0.39 (95% CI 0.25 to 0.54)	Effective
Lam <i>et al</i> 2008	24 studies with 1,092 subjects with resistant depression treated with high-frequency rTMS of left DLPFC	Response in 25% of subjects vs. in 9% and remission in 17% of subjects vs. 6% NNT for response 6 and for remission 7 Standardised mean diff. 0.48 (95% CI 0.28 to 0.69; in 21 studies)	Effective

CI – confidence interval; DLPFC – dorsolateral prefrontal cortex; ECT – electroconvulsive therapy; ES – effect size; NNT – number needed to treat; rTMS – repetitive transcranial magnetic stimulation

i.e. lower resistance to treatment. Other positive factors may, according to the authors, include also a shorter duration of the current episode and absent comorbidity with anxiety disorder (Lisanby *et al* 2009).

Treatment-related factors include stimulation intensity, frequency, the total number of pulses administered and the duration of treatment, i.e., the number of sessions. With increasing distance from the coil to the target cortex, the intensity of stimulation reaching the patient's brain decreases, which is negatively related to the anti-depressant effect of rTMS (Lisanby *et al* 2009). The influence of cortical atrophy on the distance from the coil may, according to certain authors, contribute to a lower effect of stimulation in elderly patients (Fregni *et al* 2006; Mosimann *et al* 2004; Su *et al* 2005; Aguirre *et al* 2010). It has also been proven that regional activity of the brain tends to be associated with a different response to high-frequency and low-frequency stimulation (Kimbrell *et al* 1999).

Relatively little is so far known, however, about the duration of the antidepressant effect of rTMS and its reproducibility. In 2008 a study was published that attempted to supply these missing data. It was found out in sixteen patients without medication that repeated stimulation in those who benefited from the first course of rTMS had a positive effect also in the case of repeated application. It was also stated that the duration of the antidepressant effect did differ from patient to patient, but it amounted to nearly five months on average (Demirtas-Tatlidede *et al* 2008).

REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION AND COGNITIVE FUNCTIONS

As has been mentioned above, repetitive transcranial magnetic stimulation has a minimum of adverse effects. This is also true for a potential negative impact on cognitive functions through the action of rTMS. Huang and colleagues, for instance, examined in 24 healthy volunteers the influence of unrepeated rTMS applied on the area of the left DLPFC on cognitive functions. He did not find any significant difference between the effect of active and sham rTMS on cognitive functions, yet he did record a statistically significant negative correlation of percentage shortening of choice reaction time with the age of volunteers, which may indicate that active stimulation may have greater influence on cognitive functions in younger individuals (Huang *et al* 2004). Several authors also dealt with the influence of rTMS on cognitive functions in patients with depression. No negative effect of rTMS was found e.g. by Triggs, Loo, Speer or Mosimann (Triggs *et al* 1999; Loo *et al* 2001; Speer *et al* 2001; Mosimann *et al* 2004). Several other studies, on the contrary, noted an improvement of cognitive performance. These include, for instance, a study by Klimesche and colleagues, in which they examined the impact of rTMS applied on the mesial fron-

tal and right parietal cortex, then a work by Martis and colleagues that noted the improvement of working memory, executive functions and psychomotorics following high-frequency rTMS, or a study by Moser and colleagues in which an improvement of executive functions after rTMS using 20-Hz frequency was found (Klimesch *et al* 2003; Martis *et al* 2003; Moser *et al* 2002).

In a recent overview concerning the influence of high-frequency rTMS on cognitive functions of patients with mental or neurological disorders and healthy volunteers Guse summarises, on the basis of studies performed from 1999 to 2009, that significant improvement of cognitive performance was most often caused by rTMS of frequency 10, 15 or 20 Hz applied on the area of DLPFC, with a total number of ten to fifteen sessions and of the intensity of 80–110% of individual motor threshold. At the same time he also states that patients have shown greater tendencies towards improvement than healthy volunteers (Guse *et al* 2010).

CONCLUSION

Transcranial magnetic stimulation is a relatively new method used in neurophysiological research, but also in the treatment of certain neuropsychiatric disorders. Its principle consists in influencing the brain using a changing magnetic field. For therapeutic purposes, a so-called repetitive transcranial magnetic stimulation is used in particular which can be divided into high-frequency and low-frequency. Psychiatrists have most experience with this method in the treatment of depressive disorder, but they are trying to use it in other indications as well, for example in the therapy of schizophrenia. Its advantages include good tolerability and, provided contraindications are respected, also safety.

The mechanism of antidepressant effects of rTMS has not been fully elucidated yet. According to pre-clinical studies, rTMS normalises the function of the hypothalamic-pituitary-adrenal axis, influences neurotransmitter systems, can have a neuroprotective effect and on the whole it can be said that its effects are similar to those of ECT. Clinical studies, in their turn, have proven its impact on cortical excitability and the metabolic activity of neurons.

A number of studies have been carried out dealing with the effectiveness of rTMS in the therapy of depression. Daskalakis divides them into three generations: the first one, according to him, includes older studies with a maximum of ten sessions, the second one comprises studies with more than ten sessions and, finally, the third generation covers studies using some kind of innovative approach, such as bilateral stimulation. The studies performed have also been processed in several meta-analyses, the majority of which confirmed statistically significant effectiveness of rTMS in comparison with control cohorts and, more recent meta-analyses in

particular, also good clinical effectiveness of this therapeutic method, even in patients resistant to treatment.

The predictors of the effectiveness of rTMS include, according to research conducted so far, mainly a lower resistance to treatment, shorter duration of the current depressive episode and, according to certain data, also a lower age of patients and the absence of a comorbid anxiety disorder. The duration of the antidepressant effect following rTMS is not accurately known, but can be roughly estimated at several months, with the probability that this effect can be induced again using repeated stimulation.

It can thus be concluded that repetitive transcranial magnetic stimulation represents a method of choice in the treatment of depression, even though further studies are needed in order to provide more accurate data on the mechanism of its action, help optimise the stimulation parameters and select patients who would derive greatest benefit from this therapeutic method.

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