

Transcranial magnetic stimulation in treatment of various psychiatric disorders – review of the most prominent studies and the latest news

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Summary

The aim of this paper was to present the current use of repetitive transcranial magnetic stimulation (rTMS) in psychiatric disorders with the mode of its application and results of most prominent studies. The most robust data concerns its use in major depressive disorder, while in other psychiatric disorders results are preliminary. TMS with the development of new techniques and new treatment protocols has a potential to become a very useful treatment tool in pharmacoresistant patients or patients intolerant of pharmacotherapy.

Key words: transcranial magnetic stimulation, psychiatric disorders, depression

Introduction

Transcranial magnetic stimulation (TMS) is based on Faraday's law of electromagnetic induction that states that change in intensity of current flowing in one coil induces current flow in other coil via magnetic field. In case of TMS current is induced in ion environment such as neural tissue. In 1985 Barker et al. constructed magnetic stimulator strong enough to stimulate motor cortex and cause contraction of small hand muscles [1]. It was the beginning of a very dynamic development of TMS as a tool for examination of brain's function, neurophysiology and therapeutics. In that last application TMS is used in repeated series of magnetic pulses (repetitive transcranial magnetic stimulation – rTMS). On the basis of the frequency of impulses there is division into high frequency rTMS (> 1 Hz) and low frequency TMS (\leq 1 Hz) increasing and diminishing cortex excitability respectively [2]. The application of TMS in repeated pulses is supposed to cause longer lasting changes in brain's func-

tion which result from long lasting synaptic potentiation or depression [3]. rTMS is a non-convulsive, focal, circuit-based approach [4].

Initially rTMS research concentrated on depression [5–7], a few years later the first paper concerning an application on this method in auditory hallucinations was published [8, 9]. Further rTMS research gradually involved negative symptoms of schizophrenia, obsessive-compulsive disorder, substance addiction, cognitive disorders and others. This paper presents the most important information concerning application and efficacy of rTMS in selected psychiatric disorders.

Affective disorders

The largest number of studies concerns application of rTMS in major depressive disorder. Typical place of stimulation is dorsolateral prefrontal cortex. Repeated stimulation in this area is thought to restore normal functioning of prefrontal and limbic regions implicated in mood regulation [10, 11]. Most of studies was based on supposed diminished function of left dorsolateral prefrontal cortex in depression and this place was fixed as standard for high frequency magnetic stimulation and respectively right prefrontal dorsolateral cortex for low frequency magnetic stimulation. This view is now regarded as significantly simplified and it can be thought that at least in some patients stimulation of other regions would increase effectiveness of the method [12, 13].

Among many studies in patients with major depressive disorder there are two multicenter sham-controlled studies of particular importance [14, 15]. O'Reardon et al. demonstrated that significantly more people remitted after six week of active treatment in comparison with people in control group. Remission and response rates were respectively 16% and 25%. Results of this study were basis for the authorisation in October 2008 by American Food and Drug Administration (FDA) of a device which was used for rTMS treatment in patients with major depressive disorder who failed to respond to one antidepressant medication at sufficient dose and duration. In the study conducted by George et al. remission occurred in 14.1% of patients in the group with active treatment and in 5.1% of patients in the group receiving sham stimulation, and mean time of treatment was 5.2 weeks. In open label phase of the study remission occurred in 30.5% of patients in mean time of six weeks [16]. The result is considered as better than application of next antidepressant drug in patients with similar number of previous unsatisfactory treatment trials in current depressive episode [17]. In interpretation of studies with sham stimulation in control group it is underlined that it is difficult to provide adequate placebo in application of this method [18].

Efficacy of rTMS principally in population with major depressive disorder was confirmed in open label trials. Carpenter et al. evaluated severity of symptoms in Clinical Global Impressions (CGI) and in a group of 307 subjects remission and response rates were respectively 37% and 58% [19]. Results of study conducted by Connolly et al. were in general similar, moreover, it included small group of patients with bi-

polar depression [20]. Remission and reaction rates in this group were lower than in patients with major depressive disorder, probably due to higher treatment resistance in this group.

There are also reports on long term efficacy of rTMS as well as maintenance treatment [21, 22].

The only approved indication for rTMS use is major depressive disorder. In the United States the method is applied routinely and patients may count on reimbursement of six weeks of treatment and some taper sessions. In the European Union accessibility to this method is raising. Patients may have the use of it apart from private sector and treatment may be to some extent financed from public resources i.a. in the Great Britain (recently there was created the first Treatment Service financed by National Health System – Nottingham Neuromodulation Unit).

There are only a few trials on efficacy of rTMS in patients with bipolar depression [23–25]. In the recent study of Dell’Osso in 6 among 11 participating patients occurred reaction to treatment defined as Hamilton Depression Rating Scale score endpoint reduction of at least 50% [26].

In Poland there has been published only one study on rTMS in patients with major depressive disorder. Zyss et al. have not found significant antidepressant efficacy of rTMS [27]. The detailed description of TMS studies conducted by researchers in Krakow is to find in comprehensive monograph [28].

There are examined strategies for improving the efficacy of TMS. They include bilateral sequential stimulation [29] and increased number of stimuli [30]. There are conducted studies with the use of coils allowing for deeper stimulation of brain cortex (deep transcranial magnetic stimulation-dTMS) [31]. In January 2013 FDA authorised dTMS device for treatment patients with pharmaco-resistant depression. The results of multicentre trial on this method in aforementioned population have not been published in scientific press and are known only from manufacturer’s press release. There is also search for other places of stimulation e.g. prefrontal dorsomedial cortex [32]. Recently there have been began studies on TMS synchronized with individual alpha frequency (synchronized TMS – sTMS) in patients with major depressive disorder [33].

Schizophrenia

Due to the diverse clinical presentation of schizophrenia, research on therapeutic use of rTMS concentrated separately on positive symptoms (particularly auditory verbal hallucinations) and negative symptoms.

It is thought that occurrence of auditory hallucinations comes from hyperactivity in the left temporo-parietal cortex [34]. Stimulation of this area at frequency of 1 Hz turned out to be effective in reduction of frequency and intensity of auditory verbal hallucinations in treatment-resistant patients [8, 9]. The results of further studies are equivocal. Although in the most recent meta-analysis it was described that rTMS at frequency of 1 Hz applied at area mentioned above has significant efficacy, also

in population of treatment-resistant patients (most of the studies included treatment resistant patients) [35].

Reduced frontal activation observed in people with negative schizophrenia symptoms [36] became the basis for trials of application of high frequency rTMS at dorsolateral prefrontal cortex. Cohen et al. in their pilot study, demonstrated small reduction of negative symptoms after stimulation at frequency of 20 Hz at area C3 and C4 according to 10-20 system (EEG) in six patients with chronic schizophrenia [37]. In the following two studies with the use of sequential bilateral stimulation real stimulation was not better than sham stimulation in reduction of negative symptoms [38, 39]. Given the results of currently available studies it seems that high frequency stimulation applied in left prefrontal cortex is the most effective approach towards negative symptoms of schizophrenia [40, 41]. However, the effect size in meta-analysis performed up to date indicate moderate or mild efficacy of this method. Although there has been preformed small number of research, the groups o participants were small and parameters of applied stimulation varied [41–43].

Obsessive-compulsive disorder

Although the aetiology and pathophysiology of obsessive-compulsive disorder (OCD) are not fully known, a growing evidence suggests that there are dysfunctions in the orbitofronto-striato-pallido-thalamic circuitry including the dorsolateral prefrontal cortex, orbitofrontal cortex, medial prefrontal cortex, anterior cingulate gyrus, supplementary motor area and basal ganglia [44]. Greenberg et al. were first to use rTMS in patients with OCD in 1997. They administered high frequency stimulation to the left and right dorsolateral prefrontal cortex or to mid-occipital cortex. Compulsions were significantly decreased for eight hours after right side stimulation [45]. In the most recent meta-analysis including 10 randomized controlled trials with sham stimulation rTMS applied to dorsolateral prefrontal cortex did not cause significant improvement measured in Yale-Brown Obsessive Compulsive Scale (Y-BOCS) [46]. In contrast, results of trials on low frequency at orbitofrontal cortex and supplementary motor area are promising [46]. There are only few such studies and they include small number of patients [46–49].

Alzheimer's disease

Numerous studies on rTMS effects on cognitive functions in healthy subjects were performed [50]. The discussion of these studies is beyond the scope of this paper. However, only few trials have been conducted in subjects with Alzheimer's disease (AD). Cotelli et al. observed improvement in auditory sentence comprehension in patients with moderate AD after two weeks of high frequency rTMS applied to dorsolateral prefrontal cortex [51]. Ahmed et al. demonstrated that high frequency sequential bilateral stimulation during five consecutive days gave significantly bet-

ter improvement than low frequency and sham stimulation in subjects with mild and moderate dementia [52]. The severity of symptoms was assessed using Mini Mental State Examination (MMSE), Instrumental Daily Living Activity Scale (IDLAS) and Geriatric Depression Scale (GDS). In an open label study Bentwich et al. investigated the effects of rTMS together with cognitive training [53]. They applied high frequency stimulation in six distinct regions located with the aid of MRI: Broca's area and Wernicke's area (language functions), right and left dorsolateral prefrontal cortex (judgment, executive functions, and long-term memory) and right and left parietal somatosensory association cortex (spatial and topographical orientation and praxis). There was observed a significant improvement in Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) after six weeks of treatment and four and half months of maintenance sessions. It may suggest that rTMS allow to restore brain functions and to recruit compensatory neuronal networks [54]. rTMS in combination with cognitive training may turn out to be promising and safe approach in helping people with Alzheimer's disease [55].

Addiction

In neurobiological studies there was established association between the use of psychoactive substances and the development of addiction and increase in dopaminergic activity in the mesocorticolimbic system [56]. Chronic use of psychoactive substances is thought to dysregulate mesolimbic [57] and prefronto-striatothalamic systems [58]. During withdrawal dopaminergic activity is reduced and it is associated with increased craving and risk of relapse [59]. It was shown that stimulation of the prefrontal cortex increases dopamine concentration in the caudate nucleus [60]. It is possible that even such a transient increases in dopamine release may reduce levels of craving [61]. It is thought that stimulation may influence changes arising in the brain reward system due to chronic use of psychoactive substances, as well as improve inhibitory influence of prefrontal cortex on their use [62].

In a pilot study with randomization and sham stimulation Johann et al. investigated if rTMS applied over left dorsolateral prefrontal cortex may influence tobacco craving [63, 64]. Its levels were assessed using a visual analogue scale. Participants who received real stimulation reported decreased levels of tobacco craving after single session which was the only part of the study. Following this study, Eichhammer et al. demonstrated decrease in the number of cigarettes smoked in six hours following rTMS session [65]. Amiaz et al. conducted a study including more participants, they applied ten sessions followed by one session per week during the next month, as well as exposure to smoking cues [66]. They observed that rTMS reduced cigarette consumption and levels of dependence, as well as craving induced by smoking cues, nevertheless the effect was not long-lasting.

In subjects with cocaine dependence Camprodon et al. found reduced cocaine craving after a single session of high frequency rTMS to the right dorsolateral pre-

frontal cortex, but not to the left [67]. In other study including ten sessions of high frequency rTMS to the left dorsolateral prefrontal cortex gradual reduction of craving was observed [68].

Mishra et al. demonstrated reduction in alcohol craving as a result of ten high frequency rTMS at right dorsolateral prefrontal cortex [69]. Herremans et al. examined the effect of a single high frequency rTMS session at right dorsolateral prefrontal cortex on alcohol craving just after the session (took place on Friday) and during the following weekend [70]. Reduction in alcohol craving was not observed. Maybe only one single session could not result in long-lasting changes [71].

Recapitulation

The most prominent data from clinical trials and everyday clinical practice is gathered for rTMS use in subjects with major depressive disorder. In this group of patients there is accepted protocol of treatment and guidelines.

Trials conducted in other groups of patients presented in this article were less numerous and smaller; the use of rTMS still has experimental character. In the majority of cases rTMS was applied as an add-on therapy to the ongoing unsatisfactory treatment. In all abovementioned groups of patients there is still search for the best regions for stimulation, most effective protocols of treatment as well as predictive factors of treatment response. There are also some trials on treatment of people with other psychiatric disorders than those mentioned above (e.g. eating disorders, posttraumatic stress disorder). There are ongoing multicentre trials on deep transcranial magnetic stimulation (dTMS) in various psychiatric disorders. Taking all these together, TMS may become very useful approach to the treatment of people with treatment resistant psychiatric disorders or not tolerating pharmacological treatment, but this issue surely needs further studies.

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