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BRIEF REPORT

Randomised sham-controlled study of high-frequency bilateral deep transcranial magnetic stimulation (dTMS) to treat adult attention hyperactive disorder (ADHD): Negative results

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ABSTRACT

Objectives: Recent studies support the possible effectiveness of repetitive transcranial magnetic stimulation (rTMS) as a treatment for attention deficit hyperactivity disorder (ADHD). The objective of this study was to evaluate the safety and possible efficacy of bilateral prefrontal deep rTMS for the treatment of adult ADHD.

Methods: Twenty-six adult ADHD patients were randomised blindly to sham or actual deep TMS (dTMS). Twenty daily sessions were conducted using the bilateral H5 dTMS coil (Brainsway, IL) in order to stimulate the prefrontal cortex at 120% of the motor threshold at high frequency. For assessment, Conners' Adult ADHD Rating Scale questionnaire and a computerised continuous performance test, Test of Variables of Attention, were used.

Results: No differences in clinical outcomes were detected between the actual dTMS and sham groups.

Conclusions: The presented evidence does not support the utility of bilateral prefrontal stimulation to treat adult ADHD. Due to the small sample size, caution must be exercised in interpreting our preliminary findings.

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deep TMS; ADHD; transcranial magnetic stimulation; bilateral stimulation; adult attention deficit hyperactive disorder

Introduction

Attention deficit hyperactivity disorder (ADHD) is a common neurobehavioral disorder in which the clinical manifestations are suspected of having evolved from difficulties in attention and executive functions (Doyle et al. 2005; Kessler et al. 2006). Neuroanatomical and neuroimaging studies in patients with ADHD point to fronto-striatal circuit abnormalities (Kasperek et al. 2015). The most common pharmacotherapy used for ADHD are psychostimulants (mainly different preparations of methylphenidate and amphetamine derivatives). These medications are effective and lead to the improvement of both symptoms of inattention and hyperactivity/impulsivity. However, adherence to pharmacotherapy is limited due to side effects and inefficacy for some patients (Adler and Nierenberg 2010; Sobanski et al. 2014).

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive and safe brain stimulation technique that uses brief, intense pulses of electric current

delivered to a coil placed on the subject's head in order to generate an electric field in the brain via electromagnetic induction. The induced electrical field modulates the neural transmembrane potentials and, thereby, neural activity. The effect is determined by the intensity, frequency, and number of pulses applied; the duration of the course; the coil location and, possibly, the type of coil used. In general, high-frequency (>5 Hz) rTMS promotes cortical excitability, while low-frequency (≤ 1 Hz) rTMS inhibits cortical excitability (Rossi et al. 2009; Lefaucheur et al. 2014). Deep TMS (dTMS) is a modification of standard TMS that enables deeper non-invasive cortical stimulation at an effective depth of approximately 3 cm depending on the coil's design and the stimulation intensity (Zangen et al. 2005). Both standard and deep-TMS directed to the prefrontal cortex are Food and Drug Administration-approved for the treatment of drug-resistant major depressive disorder and have gained worldwide attention as possible therapeutic tools for various neurological conditions (Bersani et al. 2013).

Studies of the pathophysiology of ADHD have revealed hemispheric asymmetry that possibly distinguishes ADHD patients from controls (Shaw et al. 2009; Keune et al. 2011). A recent meta-analysis of whole-brain voxel-based morphometry or functional magnetic resonance imaging studies during inhibitory control included 27 studies and showed that, in comparison to controls, subjects with ADHD presented under-activation predominantly in the right ventrolateral prefrontal cortex (Norman et al. 2016). Thus, pilot studies of rTMS have suggested that right dorsolateral prefrontal activation can be useful in treating ADHD (Bloch et al. 2010; Weaver et al. 2012). Although a case report indicated a possible deleterious effect of this intervention on mood, it also indicated the beneficial effect of left dorsolateral prefrontal stimulation on both mood and attention (Ustohal et al. 2012). In addition, studies using rTMS activation of the left prefrontal cortex to treat depression reported a beneficial effect on cognitive functions (Tortella et al. 2014). Based on the possible beneficial effect of both right and left prefrontal activation on cognitive functions and the possible deleterious effect on mood of right hemispheric stimulation alone, we set forth to evaluate the applicability, safety and possible efficacy of bilateral rTMS using an advanced deep coil for the treatment of adult ADHD.

Material and method

Twenty-six adults (ages 31.6 ± 6.55) suffering from ADHD (males = 14) were recruited from ADHD clinics and the community. After completing the informed consent process, the participants' diagnoses were verified via a clinical evaluation based on both DSM 5 criteria and relevant questionnaires including The Wender Utah ADHD Rating Scale and the Adult ADHD Self Report Scale (Rosler et al. 2006). In the semi-structured clinical interview, a psychiatrist who is experienced in evaluations of adult ADHD systematically assessed all ADHD criteria, and key symptoms of psychosis, affective disorders, anxiety, posttraumatic stress disorder, obsessive compulsive disorder, autistic spectrum personality disorder, and alcohol and substance abuse. Exclusion criteria included a neurological or additional psychiatric disorder that the participant was currently suffering from. During the study, subjects were prohibited from taking any neuropsychiatric medications starting from at least 48 h before their baseline assessment and continuing until their follow-up evaluation. The study was approved by the hospital's institutional review board and was registered as NCT01723319.

Table 1. Comparison of baseline characteristics of dTMS- and sham-treated patients for those completing the study.

	TMS group	Sham group	<i>P</i> value (<i>P</i> < 0.05)
<i>N</i>	9	13	
Age (average)	32.11y + 6.47	30.85y + 6.82	NS ^c
Gender	Male 6 (66.6%)	Male 8 (61.5%)	NS ^d
Academics ^a	9 (100%)	11 (84.6%)	NS ^d
Occupation ^b	6 (66.6%)	8 (61.5%)	NS ^d
ASRS	40.50 + 7.28	38.61 + 14.5	NS ^c
WUTA	1.495 + 0.43	1.474 + 0.30	NS ^c
CAARS	79.00 + 3.02	77.00 + 3.22	NS ^c
TOVA	-5.25 + 1.51	-1.41 + 1.26	NS ^c

^aAcademic education (more than 12 years of school).

^bBeing employed for at least 20 h per week.

^cNS non-significant t-test.

^dNS non-significant Chi-square test for non-parametric variables.

ASRS, Adult ADHD Self-Report Scale; WURS-The Wender-Utah Rating Scale; CAARS, Conners' Adult ADHD Rating Scale total score; TOVA, Test of Variables of Attention total score.

Patients were allocated in a randomised double-blind placebo-controlled manner to dTMS (*N* = 12) or sham (*N* = 14) treatments of bilateral pre-frontal stimulation. Four patients did not reach the post-baseline evaluations (one patient did not attend any of the treatment sessions; two patients withdrew consent after one session because of the inconvenience of attending; and one patient withdrew after five sessions due to post-treatment headaches). Thus, the efficacy analysis included nine patients who underwent the actual treatment and 13 patients who underwent the sham treatment (view Table 1 for more baseline details). Similar to the TMS protocols used for depression, 20 daily dTMS sessions (Sunday to Thursday weekly, in accordance with the standard Israeli work-week) were conducted for four consecutive weeks, using a dTMS H5 coil (Brainsway, IL; Figure 2) located over the prefrontal cortex bilaterally. Each session consisted of 55 trains of pulses at 18 Hz (2 s per train, with a 20-s inter-train interval) and an intensity of 120% of the measured motor threshold (MT, which is defined based on a visually inspected twitch of the abductor pollicis brevis). The coil was located 6 cm rostral to the motor cortex, and the total number of pulses was 1980 per session.

Evaluations were performed at baseline; after the tenth session (only for Test of Variables of Attention (TOVA)); after the twentieth session (end-point); and a week after treatment completion (follow-up). Evaluations included Conners' Adult ADHD Rating Scale (CAARS) questionnaire (Rosler et al. 2010), a self-report commonly used to monitor ADHD symptomatology, and a computerised continuous performance test, the TOVA, which is often used to monitor therapeutic effects in ADHD (Manor et al. 2008).

Two-way mixed ANOVA designs were used for statistical analysis, concerning the independent variables

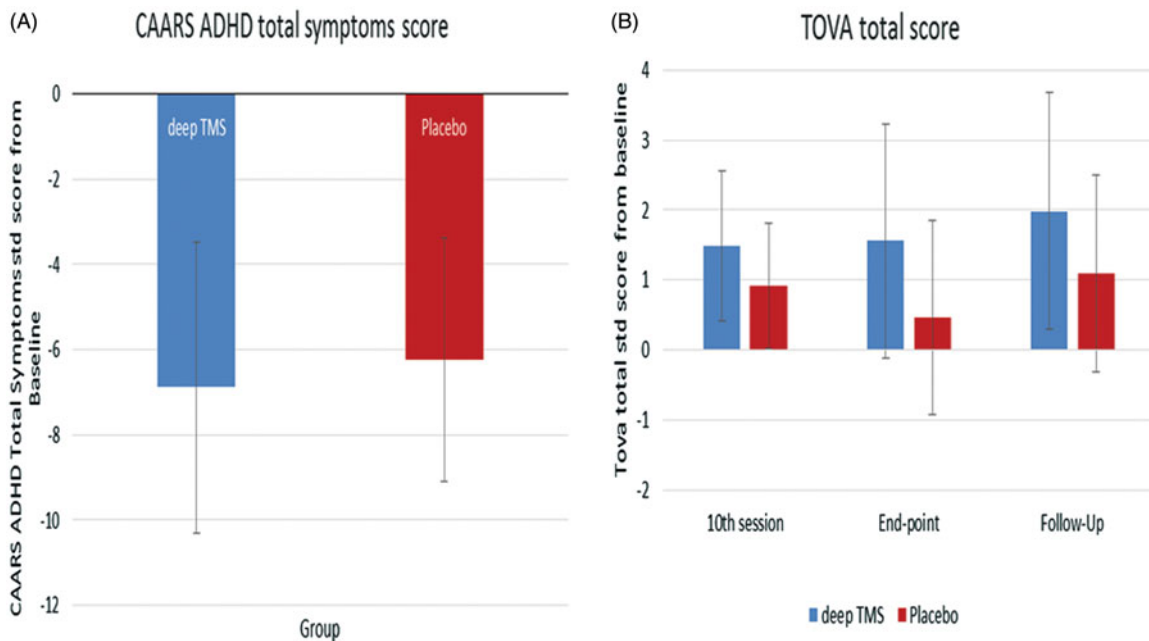


Figure 1. Conners' Adult ADHD Rating Scale (CAARS) questionnaire and the Test of Variables of Attention (TOVA) evaluations of adult ADHD (dTMS vs placebo). (A) According to CAARS ADHD total symptom standard score from baseline evaluations, the deep TMS treatment group (blue bar) did not differ from the sham/placebo group (red bar) in the averaged standard scores from the baseline. However, with both groups, the clinical symptoms were found to improve over time. (B) According to TOVA evaluations, dTMS treatment (blue bars) did not differ from sham/placebo treatment (red bars) in averaged standard scores from the baseline. That is, no improved performances were found in either group over time.

of treatment (dTMS and sham), time and interaction effects. TOVA time levels included: baseline, tenth session, end-point and follow-up. CAARS time levels compared baseline and end-point performances.

Results

In general, there were no between-group differences in any of the measures.

According to CAARS, the primary outcome measure was an improvement over time in both the actual therapy group and the sham therapy group, with no difference between the groups (Figure 1): treatment, $F(1,20) = 0.148$, $P = 0.704$, $\eta^2_{\text{partial}} = 0.01$; time, $F(1,20) = 8.688$, $P < 0.01$, $\eta^2_{\text{partial}} = 0.3$; treatment \times time, $F(1,20) = 0.022$, $P = 0.883$, $\eta^2_{\text{partial}} = 0.001$). The means (and SEM) for the dTMS group at baseline and end-point were 79.00 (3.02) and 72.11 (4.34), respectively, and for the sham group 77.00 (3.22) and 70.77 (3.05), respectively.

As reflected in the main subscales, the TOVA total score revealed no improvement over time, a marginal difference between the groups, and no interaction (Figure 2): treatment, $F(1,20) = 3.36$, $P = 0.08$, $\eta^2_{\text{partial}} = 0.14$; time, $F(3,60) = 1.267$, $P = 0.29$, $\eta^2_{\text{partial}} = 0.06$; treatment \times time, $F(3,60) = 0.16$, $P = 0.92$, $\eta^2_{\text{partial}} = 0.01$. Treatment was safe and there were no significant

side effects. The means (and SEM) for the dTMS group at baseline, tenth session, end-point and follow-up were: -5.25 (1.51), -3.76 (1.86), -3.69 (2.05) and -3.27 (1.83), respectively, and for the sham group -1.41 (1.26), -0.49 (0.84), -0.95 (1.27) and -0.31 (1.07), respectively.

Discussion

A beneficial effect of bilateral deep rTMS on adult patients suffering from ADHD was not found in the current randomised double-blind study. The fact that ADHD questionnaires (CAARS) indicated no difference between the actual and the sham group in terms of beneficial effects provided probably supports the existence of a substantial placebo effect. The computerised continuous attention test (TOVA) showed no improvement in either group. As the study was based on a small sample size, and thus has limited statistical power, the results should be generalised cautiously to the adult ADHD population. Nevertheless, it is important to state that the effect size of the 'treatment \times time' interaction was very weak for both of the evaluation measures, explaining 1% or less of the variability (partial η^2 squared is the nonlinear equivalent of R^2). Given the fact that rTMS therapy is quite demanding, and pharmacotherapy for ADHD has

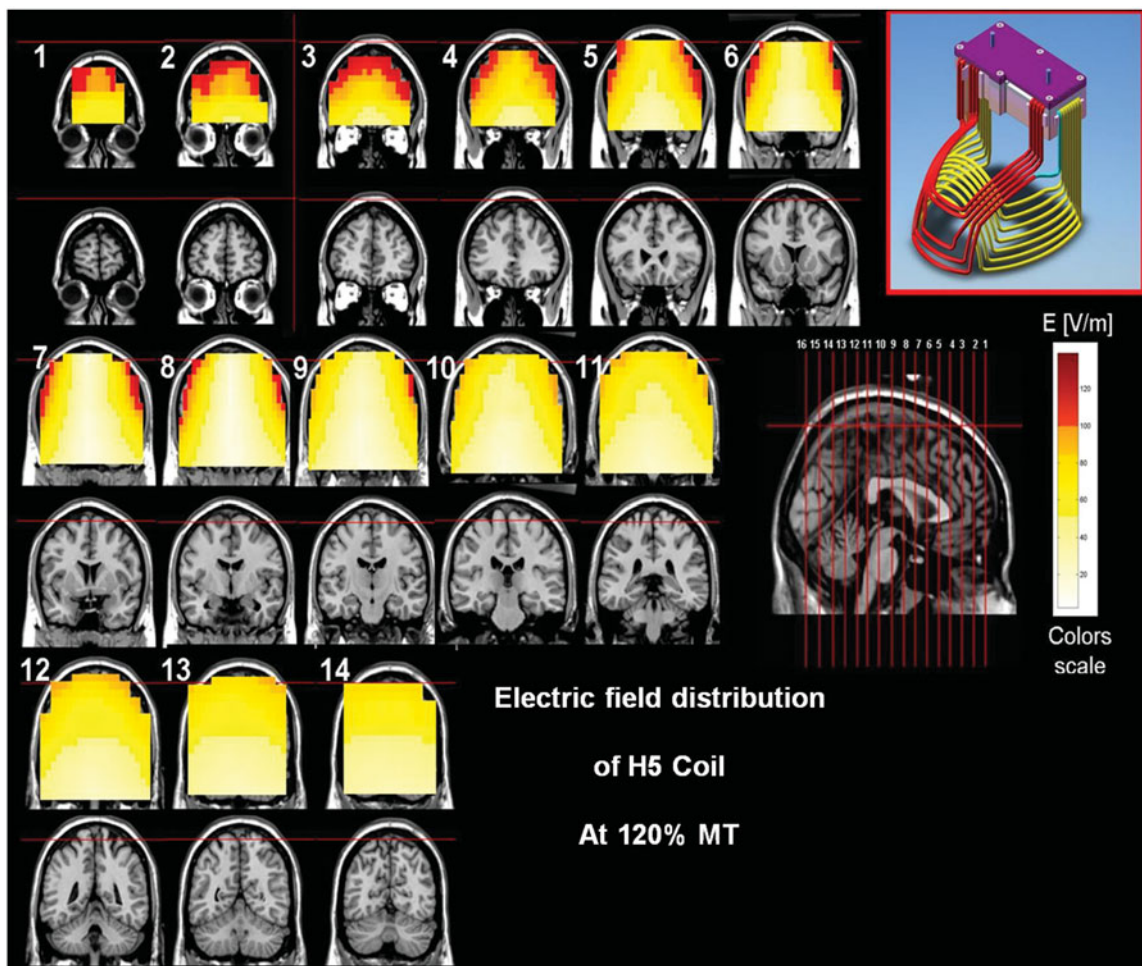


Figure 2. Coloured field maps for the H5 coil, indicating the electric field's absolute magnitude in each pixel at 100% of leg motor threshold, for 14 coronal slices, 1 cm apart. Red pixels indicate regions with field intensity above the threshold for neuronal activation, which was set at 100 V/m.

been proven effective in clinical practice, we would suggest that only a large effect of rTMS would be cause for undertaking such a major treatment change.

A previous crossover study using the usual rTMS coil to the right prefrontal cortex at 100% MT, set at 10 HZ, with 2000 pulses per day over ten treatment days, presented similar results: i.e., patients reported improvement in both the sham and the actual groups (Weaver et al. 2012). However, another blinded crossover study of a single treatment day applying the figure-of-eight rTMS coil to the right prefrontal cortex at 100% MT, set at 20 HZ, with 1680 pulses, reported improvement specifically on the actual group day but not on the sham group day (Bloch et al. 2010).

Thus, in this negative-result report, it seems that the location of coil placement should be stressed. The current study examined the use of a bilateral H5 coil, designed to produce three-dimensional distribution of electric fields (deep stimulation), directed to lateral and medial pre-frontal (up to 4 cm deep) areas

(Roth et al. 2007). In studies of TMS for depression, the type of modulation used (high or low frequency) on the right or left prefrontal cortex is crucial. Specifically, it is the high frequency stimulation of the left dorsolateral prefrontal cortex or low frequency stimulation of the right dorsolateral prefrontal cortex that are effective antidepressants (Richieri et al. 2012). This point is quite possibly relevant for ADHD as well. Importantly, both an anatomical and a functional malfunction have been found to be related to the right frontal circuits in patients with ADHD, thus supporting the use of right unilateral activation for therapy (Shaw et al. 2009).

Conclusion

Deep rTMS is safe and feasible for the treatment of adult patients with ADHD. The presented evidence, however, does not support the utility of bilateral deep rTMS activation in treating adult ADHD. That said, due to the small size of the current sample and the novelty

and complexity of the parameters studied we would also emphasise that it is important not to generalise from these results before conducting additional larger studies. We would recommend utilising a combination of clinical and cognitive tests as outcome measures.

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Disclosure statement

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