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BRIEF REPORT

Positive effects of repetitive transcranial magnetic stimulation on attention in ADHD Subjects: A randomized controlled pilot study

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Abstract

Objectives. Repetitive transcranial stimulation (rTMS) affects dopaminergic secretion in the prefrontal cortex. Attention deficit hyperactivity disorder (ADHD) had been suggested to involve dopaminergic prefrontal abnormalities. *Methods.* In this crossover double-blind randomized, sham-controlled pilot study, patients diagnosed as having adult ADHD received either a single session of high-frequency rTMS directed to the right prefrontal cortex (real rTMS) or a single session of sham rTMS. *Results.* A total of 13 patients (seven males, six females) who fulfilled the criteria for adult ADHD, according to DSM-IV criteria gave informed consent and were enrolled. There was a specific beneficial effect on attention 10 minutes after a real rTMS course. The post-real rTMS attention score improved significantly (M=3.56, SD=0.39) compared to the pre-real rTMS attention score (M=3.31, SD=0.5) [$t(12)=2.235$, $P < 0.05$]. TMS had no effect on measures of mood and anxiety. The sham rTMS had no effect whatsoever. *Conclusions.* Our findings should encourage future research on the possibility of amelioration of attention difficulties in patients suffering from ADHD by using high frequency rTMS directed to the right dorsolateral prefrontal cortex. (NIH registry NCT00825708)

Key words: *Neuroimaging, rTMS, ADHD, attention, right dorsolateral prefrontal cortex*

Introduction

Attention deficit hyperactivity disorder (ADHD) is a highly prevalent condition that impacts the affected individual throughout life (Acosta 2000; Castellanos and Acosta 2002; Arnsten 2006). Neuroanatomic and neuroimaging studies in patients with ADHD point to fronto-striatal circuit abnormalities, mainly in the right hemisphere (Castellanos and Acosta 2002; Arnsten 2006). Stimulants of the nervous system through mediation of the dopamine system comprise evidence-based therapy for ADHD (Mészáros et al. 2009). Stimulants, however, have multiple side effects that limit usage and adherence in many cases (Kociancic et al. 2004). Transcranial magnetic stimulation (TMS) is a non-invasive tool that had been developed for studying the nervous system and showed promising findings of having the capability of favorably affecting neural plasticity (Acosta et al. 2002; Hallett 2001; Siebner and Rothwell 2003; Strafella et al. 2001). Recent studies have shown that repetitive TMS (rTMS) can produce effects on the dopaminergic system in healthy subjects similar to the effect of D-amphetamine (Strafella et al. 2001; Pogarell et al. 2007). TMS has also been found useful in increasing the understanding of ADHD pathophysiology (Ucles et al. 2000; Moll et al. 2000). The published literature contains only one single case report that showed a beneficial effect of 1 Hz rTMS on attention in ADHD (Niederhofer 2008).

The aim of the present pilot study was to examine a possible amelioration in ADHD symptoms by stimulating the right prefrontal cortex with a course of rTMS.

Methods

This study was approved by the local IRB and registered in the NIH (NIH registry NCT00825708). Subjects were recruited by advertisements in Tel Aviv University and Shalvata Mental Health Center. Screening included a thorough clinical interview by a psychiatrist experienced in adult ADHD diagnosis

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assisted by the Adult ADHD Self Report Scale (ASRS) and the Wender-Utah adult ADHD scale (WUAAS).

The study methodology had a crossover double blind randomized design. It consisted of two visits (Visit 1 and Visit 2) that took place one week apart. Patients were randomized to either a single real rTMS session or a single sham rTMS session at Visit 1 and they were crossed over at Visit 2. Evaluations were conducted at the beginning of each day and 10 minutes after the administration of the real/sham rTMS. The physician giving the treatment was responsible for randomization based on pre-set numbers. He was in contact with the subject only during the treatment itself.

The evaluations included:

1. The Positive and Negative Affect Schedule (PANAS) questionnaire for assessing the subjective experience at a given time (Watson et al. 1988). This is a 20-item self-report measure with subjects rating the extent to which they feel a particular emotion on a five-point scale (1 = "not at all" to 5 = "strongly"). We divided the PANAS questionnaire into four subgroups with three measures in each group (validated by Cronbach's α) as follows: the *attention* score included concentration, detachment and attention (0.734), the *hyperactivity* score included nervousness, impulsiveness and irritability (0.763), the *anxiety* score included feeling worried and frightened (0.798), and the *mood* score included feeling happy, sad and enthusiastic (0.705). We averaged the attention and hyperactivity scores in order to establish an overall "ADHD score". The reliability test of the six items (mentioned above) reached a Cronbach α of 0.788 (i.e. internal consistency). The attention, mood and "ADHD score" measures were calculated so that higher scores represented better condition, while the hyperactivity and anxiety measures were calculated so that higher scores represented worst condition. Findings from the PANAS were defined as primary outcome measures.
2. Visual analogue scales (VASs) for attention and mood. The current attention and mood states were self-reported on a scale of 1–10 (Wewers and Lowe 1990).
3. Neuropsychological battery of tests using the Cambridge Neuropsychological Test Automated Battery CANTAB testing system (Morris et al. 1987), defined as secondary outcome measures.

A Magstim super rapid stimulator and a figure 8 coil with an internal loop diameter of 7 cm were used to deliver the rTMS. The session at each of the two visits included 42 2-s, 20-Hz stimuli at a 100% motor threshold intensity, with a 30-s inter-stimulus interval. The motor threshold was measured according to the common practice of using the visible movement of the left abductor pollicis brevis muscle. The stimulation site was the right dorsolateral prefrontal cortex located by measuring 5 cm anterior to the motor threshold. The sham condition was administered using the same stimulation parameters with one wing of the figure 8 coil in contact with the scalp and at a 45° angle with respect to the head.

Data analysis

Descriptive statistics were carried out to show the distribution of demographics and clinical variables. A paired *t*-test was used for control testing of differences between the two pre-rTMS evaluations during the two visits (baseline/control), and an independent *t*-test was used for testing differences in the pre-post delta of the TMS (real/sham) sessions between the two order groups (order effect control). Analysis of repeated measures with two within-subject variables was suitable for the crossover design of the study (1, real/sham rTMS; 2, pre/post rTMS).

Results

A total of 24 subjects were screened between May 2007 and March 2009. Five subjects were excluded for not fulfilling the ADHD criteria and another five subjects were excluded due to co-morbidity (depression = 2, post-traumatic distress syndrome = 1 and substance abuse = 2). One subject withdrew consent after Visit 1 because he perceived TMS as being painful, leaving a total of 13 consenting subjects (seven males, six females) who fulfilled the criteria for adult ADHD according to DSM-IV criteria and who were entered into the study. None of these 13 patients took any stimulant agents during the study period. Five of them had been taking methylphenidate in the last year, four on a regular daily basis. Another two had taken methylphenidate in childhood. Six of the study patients had never taken stimulants.

Real rTMS was found to improve attention as evaluated by the PANAS attention score. There were significant interactions (real/sham rTMS X pre/post rTMS) [$F(1,12) = 6.516$, $P < 0.05$]. Further analysis of the interactions revealed a significantly higher attention score post-real rTMS

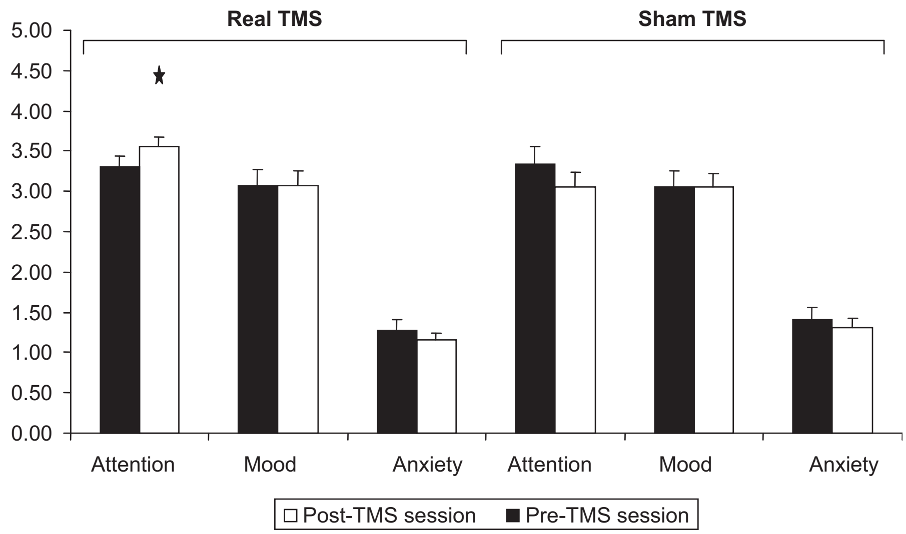

Figure 1. Improvement in attention but not in mood or anxiety after real transcranial magnetic stimulation (TMS) according to PANAS.

(M=3.56, SD=0.39) compared to pre-real rTMS (M=3.31, SD=0.5), [$t(12)=2.235$, $P < 0.05$]. No difference was found for the attention score when the pre- and post-sham rTMS results were compared. Similarly, there was no difference in the effect on mood, anxiety or hyperactivity PANAS scores between post-real/sham rTMS compared to pre-real/sham rTMS (Figure 1).

When the attention and hyperactivity scores were combined to comprise the overall "ADHD score", the interaction reached a level of significance (real/sham rTMS X pre/post rTMS), $F(1,12)=6.857$, $P < 0.05$. The "ADHD score" improved significantly following real rTMS [(M=3.96, SD=0.36) compared to pre-real rTMS (M=3.58, SD=0.46), $t(12)=3.746$, $P < 0.01$]. Sham rTMS had no effect whatsoever on the "ADHD score".

Similar findings were found on the VAS scores for attention. There was a significant interaction between real/sham rTMS and pre/post rTMS, $F(1,12)=7.57$, $P < 0.05$. The VAS score for attention improved only after real rTMS and not after sham rTMS [post rTMS session (M=7.61, SD=1.38) compared to pre-rTMS session (6.42, SD=1.85), $t(12)=2.934$, $P < 0.05$]. No such interaction or any effect was found for the VAS score for mood, indicating no change in mood following either real or sham rTMS.

There was no difference on the WUAAS and the ASRS between the subjects who had been randomized to receive real or sham rTMS on Visit 1. There was, however, a significant difference in the baseline PANAS hyperactivity score between the subjects who received real or sham rTMS on Visit 1 [$t(11)=5.66$, $P < 0.01$; $t(11)=-3.61$, $P < 0.01$, respectively], with a higher score in hyperactivity for the group that received real rTMS at Visit 1 and a lower "ADHD score" for the group that received sham rTMS at Visit 1.

Further analysis revealed that there was no difference in the pre-rTMS clinical evaluation on both visits between the randomized subjects. The cognitive neuropsychological test results (CANTAB) showed no specific profile in this group of subjects, with standard deviations at baseline that did not allow any further analysis of the effects of rTMS on these measures.

Discussion

This pilot study sought to discern whether there is a possible effect of rTMS in subjects diagnosed as having adult ADHD. The findings revealed a positive effect, albeit a modest one with questionable clinical relevance (mean change of 0.25 on a scale of 1–5), in measures of attention (as evaluated by the PANAS questionnaire and the VAS for attention) following a single session of real rTMS, using a high-frequency stimulation protocol to the right prefrontal cortex. Mood and anxiety (as measured by the PANAS mood and anxiety scores and the VAS for mood) were not affected by either sham or real rTMS, further supporting the effect of our rTMS protocol being specific to attention.

ADHD is defined as a clinical entity that is diagnosed and evaluated by means of questionnaires and clinical assessments. Results of cognitive tests on ADHD patients are heterogeneous (Willcutt et al. 2005), and so it is not surprising that cognitive functions, as assessed by a computerized battery, were too variable for systematic analysis in our small sample. We chose the dorsolateral prefrontal cortex as the stimulation site based on previous findings that described its having a major role in the pathophysiology of ADHD (Mészáros et al. 2009; Castellanos et al. 1996). There is substantial evidence from both animal and human imaging studies that rTMS has an effect on the modulation of neurotransmitters, specifically dopamine and its metabolites (e.g., homovanillic acid), mainly after prefrontal cortex stimulation (Pogarell et al. 2007; Ucles et al. 2000; Shimamoto et al. 2001). Thus, prefrontal dopaminergic stimulation is a reasonable physiological explanation for our findings.

The effect exclusive to attention and not on mood or anxiety caused by stimulating the right prefrontal cortex also adds credence to our hypothesis. We recommend the conducting of studies on larger populations to evaluate the effects of stimulation in this area, and then to compare them to the effects of stimulation in other brain regions (i.e. the left prefrontal cortex). We consider this study as being a preliminary step towards the evaluation of rTMS as a possible tool in the treatment of ADHD.

The limitations of our study are that it includes a small group of patients, is based on a subjective report and that it has a crossover design. Another limitation is that the difference in the somatosensory experience of real rTMS and sham limits the true blinding.

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Statement of Interest

No author has any biomedical function interests or potential conflicts of interest.

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