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Effects of repetitive transcranial magnetic stimulation over supplementary motor area in patients with schizophrenia with obsessive-compulsive-symptoms: A pilot study

Vauto Alves Mendes-Filho [a,*], Danilo Rocha de Jesus [b], Paulo Belmonte-de-Abreu [a], Carolina Tosetto Cachoeira [a], Maria Inês Rodrigues Lobato [a]

[a] Hospital de Clínicas de Porto Alegre (HCPA), Universidade Federal do Rio Grande do Sul, Porto Alegre (UFRGS), Rio Grande do Sul, Brazil
[b] Centre for Addiction and Mental Health, University of Toronto, Toronto, Ontario, Canada

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ABSTRACT

In patients with schizophrenia, obsessive-compulsive symptoms (OCS) are associated with lower rates of quality of life and polypharmacy. No previous controlled studies have tested the efficacy of repetitive transcranial magnetic stimulation (rTMS) on the treatment of OCS in this population. The present study examined the therapeutic effects of rTMS applied to the supplementary motor area (1 Hz, 20 min, 20 sessions) on OCS and general symptoms in patients with schizophrenia or schizoaffective disorder, and whether this intervention can produce changes in plasma levels of brain derived neurotrophic factor (BDNF). A double-blind randomized controlled trial was conducted. Active and sham rTMS were delivered to 12 patients (6 on each group). Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) and Brief Psychiatric Rating Scale (BPRS) scores, as well as BDNF levels, were assessed before, after, and 4 weeks after treatment. rTMS did not significantly change the outcomes after treatment and on the follow-up (Y-BOCS: Wald's $X^2=3.172$; $p=0.205$; BPRS: $X^2=1.629$; $p=0.443$; BDNF: $X^2=2.930$; $p=0.231$). There seemed to be a trend towards improvement of BPRS scores 4 weeks after rTMS treatment comparing with sham (Cohen's $d=0.875$, with 32.9% statistical power). No side effects were reported. Future studies with larger sample sizes are needed.

1. Introduction

Schizophrenia is a debilitating disorder that affects approximately 1% of the population worldwide (Stilo and Murray, 2010). Of these patients, approximately 10–30% develop associated obsessive-compulsive symptoms (Hadi et al., 2012). Many drugs are available for the treatment of schizophrenia and obsessive-compulsive symptoms, but the concomitant use of selective serotonin reuptake inhibitors (SSRI) with antipsychotics is associated with a higher rate of side effects and drug interactions, and should be used with caution (Buchanan et al., 2010; Hadi et al., 2012). Moreover, in recent decades, it has been observed that the use of second-generation antipsychotics, particularly clozapine, has been associated with the emergence or worsening of obsessive-compulsive symptoms (Mukhopadhaya et al., 2009; Schirmbeck and Zink, 2012; van den Heuvel et al., 2005). Research has progressively increased our understanding of the brain mechanisms underlying the various symptoms of schizophrenia and obsessive-compulsive disorder, and evidence suggests that the regions involved in the inhibitory control of undesirable thoughts or acts, such as the supplementary motor area (SMA), may be dysfunctional in patients with obsessive-compulsive disorder (OCD) (Hadi et al., 2012; Mantovani et al., 2010). Therefore, treatments aimed at modulating the activity of this area may be useful in the treatment of obsessive-compulsive symptoms in patients with schizophrenia.

Several studies have shown that cortical inhibition and excitability is altered in a number of neurological and psychiatric disorders (Barr et al., 2008; Daskalakis et al., 2007; de Jesus et al., 2011; Fitzgerald et al., 2002a, 2002b; George et al., 2003; Mantovani et al., 2006; Richter et al., 2012; Rosa et al., 2007; Wassermann and Lisanby, 2001). Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive technique that can modulate cortical inhibition and excitability (de Jesus et al., 2014). It involves the application of a small magnetic fields to the desired brain region through a coil placed on the scalp (Mantovani et al., 2010).

* Correspondence to: Rua Ramiro Barcelos, 2350 – Santa Cecília, Porto Alegre 90035-903, RS, Brazil.
E-mail address: vautomf@gmail.com (V.A. Mendes-Filho).

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The proposed mechanism underlying the effects of rTMS is the induction of local increases or decreases in cortical excitability or inhibition. Different parameters of stimulation can produce different effects (Mantovani et al., 2010). rTMS has been found to be safe in several experimental and clinical studies, and therapeutic effects have been demonstrated mainly for major depressive disorder, but also for OCD, positive and negative symptoms in schizophrenia, pain disorders, tinnitus, and motor deficits after stroke (Avenanti et al., 2012; Berlim et al., 2013; Bressan et al., 1998; Downar and Daskalakis, 2013; Freitas et al., 2009; Lefaucheur et al., 2014; Leung et al., 2009; Müller et al., 2013; Sampson et al., 2006; Shi et al., 2014; Slotema et al., 2010; Triggs et al., 2010).

Recently, rTMS has been studied for the treatment of patients with OCD (Alonso et al., 2001; Berlim et al., 2013; Gomes et al., 2012; Kang et al., 2009; Mansur et al., 2011; Mantovani et al., 2010; Prasko et al., 2006; Ruffini et al., 2009; Sachdev et al., 2007; Sarkhel et al., 2010). Berlim et al. (2013) published a meta-analysis indicating that low-frequency rTMS aiming the SMA is promising for treating OCD-related symptoms. High-frequency rTMS applied over the dorsolateral prefrontal cortex did not appear to be more effective than sham rTMS for those symptoms (Berlim et al., 2013).

Brain-derived neurotrophic factor (BDNF) is a protein that has been thoroughly investigated and is associated with neuronal protection and staging in severe psychiatric disorders (Asevedo et al., 2013; Berk et al., 2011; Fernandes et al., 2011). Several studies have shown that BDNF levels vary in patients with psychiatric disorders compared to healthy individuals, and levels increase after appropriate treatment (Brietzke et al., 2009; Cunha et al., 2006; Fernandes et al., 2011; Ricken et al., 2013). To the best of our knowledge, no previous study has investigated the increase in BDNF levels associated with rTMS in OCD.

Assuming that the pathophysiology of obsessive-compulsive symptoms in both patients with OCD and patients with schizophrenia is similar, we conducted a double-blind, sham-controlled clinical trial in which low-frequency and sham rTMS was applied to the SMA in patients with schizophrenia with obsessive-compulsive symptoms. Furthermore, BDNF levels were measured for possible correlation with the clinical outcome.

2. Methods

2.1. Subjects

Twelve patients with schizophrenia or schizoaffective disorder between 18 and 65 years of age were enrolled. The diagnoses were confirmed using the *Structured Clinical Interview for DSM-IV-TR* (SCID-I). Inclusion criteria included the presence of persistent obsessive-compulsive symptoms, with a Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score of at least 16, corresponding to a moderate symptomatology (Goodman et al., 1989a, 1989b). Exclusion criteria included a diagnosis of dementia, substance abuse, suicide risk, pregnancy, prior history of seizures, neurosurgery or head trauma, use of cardiac pacemaker or intracranial metallic clip, neurological disease, significant unstable medical condition, estimated IQ $\leq$ 80, current alcohol or drug abuse, or inability to provide informed consent. Women in fertile age must have been using an appropriate contraceptive method. A total of 12 patients were enrolled. All patients were naïve to rTMS treatments. The study protocol was approved by the Ethics Committee of Hospital de Clínicas de Porto Alegre. A signed, informed consent was obtained from every patient. This trial was submitted to ClinicalTrials.gov under the identifier NCT02105064.

2.2. rTMS protocol

Patients were randomly allocated to either rTMS or sham groups. Subjects were randomized through the website random.org, which offers a reliable and practical platform for the random allocation of individuals.

Study participants, clinical raters, and all personnel responsible for the clinical care of the patients were blind to the allocated condition and allocation parameters. A Neurosoft Neuro-MS (Neurosoft Ltd., Russia) with an angulated figure-of-eight coil was utilized in the rTMS sessions. 1 Hz rTMS was administered at an intensity of 100% of the motor threshold (MT), which was ascertained prior to the first session of each week. MT was based on visualization of trace movements in 5/10 tries when stimulating the primary motor cortex. This method has been reported to be as sensitive as EMG-based methods of detecting MT (Pridmore et al., 1998). Active and sham stimulation were administered to the SMA site according to the International 10–20 EEG electrode position system (15% of the inion-nasion distance, anterior to the vertex on the sagittal plane). There were no pauses in the stimulation trains. Sham stimulation was performed by positioning the coil on a 90-degree angle (perpendicular to the parasagittal plane) over the SMA, also at 1 Hz. This form of sham stimulation induces local sensations on the scalp similarly to the disturbances caused by the real stimulation (Praeg et al., 2005). All subjects underwent a total of 20 sessions of 20 min each, 5 sessions per week, for four weeks.

2.3. Clinical measures

Clinical assessments were conducted before the first session, immediately after the last session, and 4 weeks after the last session, and were performed by a trained psychiatrist. The primary outcome was the changes on the Y-BOCS (version I). Furthermore, psychotic symptoms were evaluated using the 18-item anchored version of Brief Psychiatric Rating Scale (BPRS-A).

2.4. BDNF levels

Immediately after the clinical assessments, blood was collected from all participants by a senior nurse without anticoagulant. Within 3 h, serum was separated by centrifugation at 3000 $\times$ G at room temperature. The supernatant was stored at -80 °C until the assay. BDNF serum levels were determined by sandwich-ELISA method using BDNF monoclonal antibodies (R&D Systems, Minneapolis, MN, USA) according to the manufacturer's instructions.

2.5. Statistical analysis

Students' *t* tests were applied to compare basal demographic, clinical and biological data between active and sham groups. The equivalences between antipsychotic dosages were calculated using the equations described by Andreasen et al. (2010). Changes in Y-BOCS and BPRS scores, as well as BDNF serum levels, were analyzed using generalized linear models and Wald chi-square tests. Cohen's *d* and statistical power were calculated for post-hoc analysis. All statistical analyses were made using IBM SPSS Statistics version 18.

3. Results

A total of 22 patients were screened. Eight patients declined due to difficulties in attending the hospital five times a week. Two individuals did not fulfill the inclusion criteria and were excluded. Twelve patients (10 male and 2 female), mean age of 41.1 $\pm$ 9.8 years, were randomized to receive either active or sham rTMS. 11