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Modulation of motor cortex excitability in obsessive-compulsive disorder: An exploratory study on the relations of neurophysiology measures with clinical outcome

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ABSTRACT

Low-frequency repetitive transcranial magnetic stimulation (rTMS) to supplementary motor area (SMA) showed clinical benefit in obsessive-compulsive disorder (OCD). Here we tested whether clinical improvement was associated with enhanced cortical inhibition as measured by single and paired-pulse TMS variables. In 18 OCD patients receiving 4 weeks of either active or sham rTMS in a double-blind randomized trial, we assessed bilateral resting and active motor thresholds (RMT and AMT), cortical silent period (CSP), short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF). We tested correlations between changes in Yale-Brown Obsessive Compulsive Scale-Self-report (Y-BOCS-SR), Clinical Global Impression-Severity subscale (CGI-S) and cortical excitability measures.

Active rTMS increased right hemisphere RMT whose change correlated with Y-BOCS-SR improvement. Baseline RMT hemispheric asymmetry, defined as the difference between left and right hemispheres RMT, and its normalization after active rTMS correlated with Y-BOCS-SR and CGI-S improvements. Active rTMS also increased right hemisphere SICI whose change correlated with Y-BOCS-SR and CGI-S at week 4, and with normalization of baseline RMT hemispheric asymmetry.

Treatment-induced changes in cortical excitability measures are consistent with an inhibitory action of SMA rTMS on dysfunctional motor circuits in OCD. Correlations of neurophysiology measures with therapeutic outcome are supportive of the role of SMA in the modulation of OCD symptoms.

1. Introduction

It has been hypothesized that malfunctioning of cortico-striato-thalamo-cortical circuitry (CSTC), and in particular deficits in inhibition of irrelevant information and response control in obsessive compulsive disorder (OCD) (Van den Heuvel et al., 2005; Chamberlain et al., 2005), may account for the reduced ability of patients to inhibit intrusive thoughts, impulses, or images and repetitive motor responses or mental rituals. This deficient inhibition has been posited to have a neurophysiologic signature, associated with a higher than normal level of cortical excitability (Leocani et al., 2001; Rossi et al., 2005).

Transcranial magnetic stimulation (TMS) measures of motor cortex excitability provide some evidence for deficient cortical inhibition in OCD. For example, the minimum magnetic field intensity required to elicit a twitch in a relaxed hand muscle, resting motor threshold (RMT), a marker of ion channel function (Ziemann et al., 1996a), is reduced in OCD compared with healthy comparison subjects (Greenberg et al., 2000). Short-interval intracortical inhibition (SICI), a marker of GABA(A)-ergic function (Ziemann et al., 1996b), has also been reported to be reduced in patients with OCD (Greenberg et al., 1998; Greenberg et al., 2000). Patients with OCD demonstrated significantly shortened Cortical Silent Period (CSP), a marker of GABA(B)-ergic function (Siebner et al., 1998), and increased intracortical facilitation (ICF), a marker of glutamatergic function (Ziemann et al., 1998), compared with healthy subjects (Richter et al., 2012).

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Consistent with these physiological findings, a neuroimaging study suggested that premotor areas, such as supplementary motor area (SMA), are hyperactive in OCD, and that this hyperactivity may relate to deficient inhibitory control of behavior (Yücel et al., 2007). Using functional magnetic resonance imaging (fMRI) with a task encompassing inhibitory control processes (the Multi-Source Interference Task), OCD patients had greater relative activation of a spatially extended SMA/dorsal anterior cingulate cortex (ACC) region (peaking in the pre-SMA), along with greater deactivation of the rostral ACC during high- versus low-conflict trials.

Given this evidence of deficient motor inhibitory control in OCD, the use of low-frequency repetitive TMS (rTMS) to enhance inhibition in motor circuits (Chen et al., 1997) may be a fruitful avenue to explore as a putative treatment. We hypothesized that the pre-SMA may be a therapeutic target for rTMS in OCD because that region is involved in cognitive aspects of internal movement generation (Picard and Strick, 2001) and with the conscious urge to act (Fried et al., 1991).

To explore the impact of rTMS on OCD symptoms and motor cortex excitability, we applied low-frequency (1-Hz) rTMS to the pre-SMA in 10 patients in an open study, and measured RMT before and after 2 weeks of open-label treatment. The 1-Hz rTMS treatment applied to the pre-SMA resulted in OCD symptoms improvement and restored physiological levels of cortical excitability in the right hemisphere, as indexed by RMT (Mantovani et al., 2006). In case reports of two additional patients with OCD and Tourette's Syndrome (TS) (Mantovani et al., 2007), we again found a significant clinical improvement and rTMS induced increase in RMT, in a direction that tended to normalize a baseline hemispheric imbalance. Analyses of clinical and neurophysiology measures in a subgroup of patients affected with TS ($n=10$) and comorbid OCD ($n=5$), and enrolled in a randomized controlled trial (RCT), showed an average reduction of 54% in the Yale-Global Tic Severity Scale (Y-GTSS), 44% in the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), and an improvement from markedly to mildly ill on Clinical Global Impression-Severity subscale (CGI-S), whose change correlated with increased right hemisphere SICI (Mantovani et al., 2012).

In a larger ($n=21$) randomized sham-controlled trial we recently reported that 1-Hz rTMS to the pre-SMA had significant benefit in treatment-resistant OCD (Mantovani et al., 2010). Here we present pre- and post-rTMS intervention measures of motor cortex excitability for that trial, and test whether rTMS clinical effects were associated with changes in RMT, AMT, CSP, SICI, and ICF. Our hypothesis was that therapeutic effect would be linked to an increase in cortical inhibition.

2. Methods

2.1. Subjects

All patients gave written informed consent, and the protocol was approved by the New York State Psychiatric Institute/Columbia University Institutional Review Board. Patients were randomly assigned in a 1:1 ratio to either active rTMS or sham, five times per week, for 4 consecutive weeks.

To be eligible patients had to be 18–70 years old, right-handed, have a primary diagnosis of OCD (confirmed via Structured Clinical Interview/SCID for DSM-IV) (First et al., 1997), current episode duration of at least one year, have clinically significant OCD symptoms (defined as a total Y-BOCS score of ≥ 16) (Goodman et al., 1989a, 1989b) despite treatment with an adequate trial of a Serotonin Reuptake Inhibitor (SRI) and Cognitive Behavior Therapy (CBT). An adequte SRI trial was defined as treatment for at least 12 weeks on the SRI, that meets or exceeds recommended dosage level for OCD (Koran et al., 2007). Individuals who could not tolerate, due to side effects, medications of this class at the specified dose and duration were also included. An adequate trial of CBT was defined as at least once a week for 8 weeks with clear evidence of exposure during sessions and homework given. Patients currently on medication and/or psychotherapy must have been in stable treatment for at least 12 weeks before initiation and throughout the study. Patients were excluded if they were treatment-refractory (defined as non-response to clomipramine, at least 2 selective SRIs (SSRIs) at adequate dose and duration plus CBT in the last year) and were diagnosed with severe major depressive disorder (MDD) (confirmed by SCID and measured by the Hamilton Depression Rating Scale (HDRS-24 ≥ 20)). Patients who exhibited significant acute suicide risk, or with a history of bipolar disorder, of any psychotic disorder, or of substance abuse or dependence within the past year were excluded. Patients with neurological disorders, increased risk of seizure, use of proconvulsant medications (such as bupropion, maprotiline, tricyclic antidepressants, classical antipsychotics), implanted devices, metal in the brain, unstable medical conditions, pregnancy, or breast-feeding were also excluded.

To avoid confounds on motor cortex excitability measures, medications with a known inhibitory effect on brain excitability (such as anticonvulsants, benzodiazepines, atypical antipsychotics) were not allowed. We excluded patients with prior TMS exposure to reduce risk of unblinding.

Twenty-one right handed outpatients (13 male and 8 female; mean age = 38.9 years, S.D. = 11.9) who met study criteria were recruited and randomly assigned to active or sham rTMS. Three patients (2 randomized to active and 1 to sham) were withdrawn before starting rTMS: two experienced a worsening of depression and the other fainted during the RMT determination. Therefore, analyses were conducted on the 18 completers (nine in the active and nine in the sham group); demographics and clinical characteristics of this sample are shown in Table 1.

2.2. Concomitant medications

Six of 18 patients were medication free, while the remaining 12 were on medications held stable for 3 months prior and throughout the trial. Five patients were on fluoxetine (average dose = 76 mg/d), two on escitalopram (average dose = 30 mg/d), two on citalopram (average dose = 60 mg/d), one on fluvoxamine (average dose = 300 mg/d), and two on sertraline (average dose = 225 mg/d). Five patients continued receiving supportive psychotherapy at a stable frequency during the trial.

2.3. Outcome measures

Patients were evaluated every 2 weeks by raters (HBS, BAF) blind to treatment assignment, and completed self-rating forms at the end of each week of treatment. The primary efficacy measures were the Y-BOCS (Goodman et al., 1989a, 1989b), the Y-BOCS-Self-report (Y-BOCS-SR), a scale very similar to the clinician-administered rating, with excellent internal consistency and test-retest reliability (Baer et al., 1993; Steketee et al., 1996), and the CGI-Severity subscale (CGI-S) (Guy, 1976).

2.4. rTMS methods

rTMS was administered with the biphasic MAGSTIM super-rapid stimulator (Magstim Company, Ltd., Whitland, UK) using a vacuum cooled 70-mm figure-8 coil (AM). Stimulation parameters were 1-Hz, 20 min train (1200 pulses/day) at 100% of resting MT (using the lowest value of right or left hemisphere resting MTs obtained with the biphasic stimulator), once a day, 5 days a week, for 4 weeks, hence well within safety margins (Rossi et al., 2009a, 2009b). The coil was positioned over pre-SMA, targeted using the International 10-20 EEG System and defined at 15% of the distance between inion and nasion anterior to Cz (vertex) on the sagittal midline. The coil was placed with the handle along the sagittal midline, pointing towards the occiput to stimulate bilaterally and simultaneously the pre-SMA. Once the stimulation site had been determined, it was marked in the Brainsight™ (Rogue Research, Montreal, Canada) neuronavigation computer program, in order to monitor online during each session the optimal positioning of the coil, hence reducing the variability of the induced electric currents within the brain (Cincotta et al., 2010).

2.5. Masking and protection of the blind

Sham rTMS was administered using the Magstim Sham coil which contains a mu-metal shield that diverts the majority of the magnetic flux such that a minimal (less than 3%) magnetic field is delivered to the cortex. This coil looks and sounds like an active coil, however it does not feel exactly like active rTMS, which generates a stronger tapping sensation on the scalp. In order to maintain the blind, we kept the raters blinded to treatment condition and created a separation between the clinical team (HBS, BF), neurophysiology data analyst (BDB), and rTMS treating physician (AM). Specifically, the rTMS treating physician did not know if rTMS was set to active or sham; in fact, after resting MT determination, the TMS lab managers (TS, TN), who were not involved in rTMS treatment sessions, set up the active or sham coil while the rTMS treating physician was not in the laboratory. We also excluded patients who received TMS before.

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