Mohsin Ahmed
PGY-1, Psychiatry
CRC Rotation
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fMRI guided orbitofrontal cortical repetitive transcranial magnetic stimulation in treatment resistant OCD: a randomized, sham-controlled trial

A. Study Purpose and Rationale

Obsessive-compulsive disorder (OCD) is a highly debilitating neuropsychiatric condition characterized by recurrent intrusive thoughts (obsessions) and/or repetitive rituals (compulsions), often performed according to rigid rules [1]. By DSM IV criteria, these symptoms must be time-consuming and cause marked distress and impairment. Indeed, voluntary suppression of compulsive behaviors leads to high levels of anxiety, and OCD is chronically disabling within the realms of both social and occupational functioning [2]. The lifetime prevalence of OCD is estimated to be 2-3% [3] and in 1996, the World Health Organization declared OCD as one of the top 10 causes worldwide of 'years lived with illness-related disability' [2]. Indeed, the burden of OCD at a population level is considerable, as evidenced by a study in the USA which estimated the economic cost of OCD to be $8.4 billion [2].

Although the introduction of selective serotonin reuptake inhibitors (SSRIs) has improved the treatment and prognosis of OCD, a significant percentage of patients (between 40-60%) do not respond to treatment, and the response has a latency of 4–8 weeks [4]. In particular, this low rate of overall response to first-line pharmacological strategies has led to the development of several augmenting pharmacologic and nonpharmacologic strategies, including clomipramine, low doses of atypical antipsychotics, deep brain stimulation (DBS), functional neurosurgery, and repetitive transcranial magnetic stimulation (rTMS). Of these, rTMS is of particular interest given that it is a noninvasive technique. In rTMS, magnetic pulses are delivered to the cortex by means of a hand-held stimulating coil applied directly to the head. One single pulse produces an intense magnetic field that causes depolarization of lower neurons and synapses. Although the limit is several centimeters under the scalp, TMS can influence subcortical neurons with a transsynaptic mechanism, as seen in positron emission tomographic studies [5]. As opposed to a single pulse, the effects of repetitive pulses rTMS are long-lasting, presumably due to plastic changes in neuronal excitability and prolonged changes in synaptic strength [6], such as long-term synaptic plasticity [7].

To date, only a handful of studies have examined the impact of rTMS on OCD with variable results. These data show positive effects after stimulation of the right and left prefrontal cortex and of the supplementary motor area, though more recent controlled trials of prefrontal cortical stimulation failed to show any difference from the placebo/sham condition [8]. Furthermore, the small sample

sizes, considerable variability in stimulation sites, and parameters used have prevented the drawing of definitive conclusions about its clinical efficacy [4].

Interestingly, however, though most studies have focused on the dorsolateral prefrontal cortices, the dominant neurobiological model for OCD focuses on abnormalities in orbitofrontal cortex (OFC) to striato-thalamic circuits [9]. Indeed, There is convincing data suggesting that: (i) this circuit shows elevated metabolism in patients with OCD, particularly associated with expression of OCD symptoms and anxiety, (ii) the OFC is consistently reduced in volume in OCD, and (iii) that activation abnormalities are observed in these regions during fMRI in OCD patients compared with controls, as can be highlighted with cognitive tasks such as symptom provocation [2]. Though the causal relationship between these structural and functional observations has not been established, interestingly functional brain changes have been shown to be dynamic and may normalize following therapeutic approaches which also reduce OCD symptoms [2]. Therefore, targeting therapeutic brain stimulation with rTMS over the lateral OFC could be an OCD specific treatment, which may further help to definitively establish the role of OFC activity in the neurobiology of OCD, in addition to potentially alleviating in the significant population of patients resistant to first-line treatment.

However, clinical applications of rTMS place stringent requirements on the accuracy and repeatability of the specific rTMS location chosen, and the lack of this stimulation accuracy and repeatability likely accounts for some of the discrepancies on the efficacy of rTMS in the literature. Indeed, the largest source of variability in TMS studies is likely to be inaccurate coil positioning, such that a different cortical area is stimulated to the one intended by the operator [10]. Therefore, in any study of OFC rTMS, it is important to confirm and ensure that the targeted region is being activated by the rTMS coil. Fortunately, neuronavigation techniques employing both structural and functional MRI have been successfully used to improve efficacy of rTMS in depression [11] and to individual rTMS coil placement in the treatment of schizophrenia [12] and generalized anxiety [13]. Therefore, given the importance of accurately and reproducibly targeting the OFC with rTMS in OCD patients, this study proposes to employ similar neuronavigation techniques to optimize individual rTMS coil placement for lateral OFC activation elicited by established symptom provocation tasks.

B. Study Design and Statistical Analysis

The proposed study is a randomized, sham-controlled trial of OFC rTMS targeted with fMRI neuronavigation in treatment-resistant OCD. The trial will consist of a 4 week double-blind phase. Patients will be randomly assigned in a 1:1 ratio to either active rTMS arm or sham arm, 5 times per week, for 4 consecutive weeks. At the end of 4 weeks, non-responders to sham and responders (defined below) to either active or sham rTMS will be offered the option of receiving open-label rTMS for an additional 4 weeks. Responders will be invited back at 3 months

following the last rTMS to assess persistence of benefits during naturalistic follow-up [8].

The primary outcome measure will be the severity of OCD symptoms, as determined with the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), which has been standardized, validated, and is widely used in OCD research [14]. A 25% decrease in OCD symptoms as determined on this scale has previously been established as a clinical response in patients with OCD resistant to medical therapy [14]. Therefore, using conservative estimates based on previous literature in a similar patient population [8, 14], a corresponding effect size of 7 is expected, taking into consideration the low response to sham in previous rTMS studies of OCD patients [8] and that OCD patients in general have a low placebo response [15]. Based on these same prior studies, a reasonable estimate of the standard deviation in this outcome measure in such a patient population is 6. Using an unpaired t-test to compare the mean change in the primary outcome measure (treated as a continuous variable), the study will require at least 13 subjects in each arm, for a power of 80% at a p value of 0.05.

C. Study Procedure.

The entire study will last 4 weeks, and each subject is anticipated to participate for this period of time. Independent clinician evaluators blind to treatment arm assignment will evaluate patients at a baseline and at the end of the 4 weeks of treatment, with symptom severity assessed using the Y-BOCS as above.

Prior to beginning the treatment study, optimal OFC stimulation sites for each individual patient will be determined by fMRI neuronavigation. A 1.5 T magnetic resonance imaging (MRI) unit and a standard head coil (General Electric, Milwaukee, Wisconsin) will be used to obtain T2*-weighted images with a gradient echo pulse sequence (repetition time [TR], 4000; echo time [TE], 60; flip angle, 60°). To highlight brain hyperactivity during OCD symptoms, a symptom provocation task during functional imaging will be given as previously described [16]. Briefly, principal manifestations and stimulants related to obsessive-compulsive symptoms will be identified for each patient prior to scanning, such as contamination, pathological doubt, and violence. Approximately 20–30 words related to these factors will be selected through discussion with each patient. During fMRI scanning in the task condition, patients will be required to generate those words one by one in their minds every 4 sec, at the sound of a bell. Under control conditions, patients will be asked to generate names of vegetables, flowers, and fruits in their minds at the same interval. Patients will perform these tasks in the scanner using a block design paradigm in which task trial and control trial are given by turns. Each trial will comprise ten 40-sec periods (total, 400 sec) in which control and task conditions are alternated. On the basis of this symptom provocation task, individual fMRI maps overlaid on structural MRI images will be generated using standard methods [16].

Upon identification of the optimal OFC hyperactive region for each patient, the rTMS stimulation coil will be positioned over this site by a frameless stereotaxis, allowing for the co-registration of the rTMS coil with the patient's MRI scan, with the fMRI results overlaid upon the three-dimensional (3-D) rendered structural scan. Patients will be given a 4 second trial stimulation at 1 Hz (using the parameters below) while performing the control task above during another fMRI scan to confirm that the targeted region is optimally activated by stereotaxic coil placement. This will allow for the rTMS coil to be reproducibly navigated with anatomical precision during each subsequent rTMS treatment session.

During the trial, rTMS will be administered to patients in the treatment group using parameters previously employed in OCD studies [8]: 1-Hz, 20-min train (1200 pulses/day) at 100% of resting motor threshold (using the lowest value of right or left hemisphere) per hemisphere, once a day, 5 days per week for 4 weeks. Sham rTMS will use a similar coil with a metal insert blocking the magnetic field and scalp electrodes that deliver matched somatosensory sensations. Such a sham coil has recently been shown to prevent unmasking and keep administrators and patients blinded to treatment arm [17]. Therefore, both real treatment and sham coils will give rise to clicking sounds and result in somatosensory tapping sensations at the stimulation scalp site.

D. Study Drugs*
None

E. Medical Device.*
rTMS treatment will be delivered using a commercially available Magstim super-rapid stimulator (Magstim Company Ltd, UK) using a vacuum cooled 70-mm figure-of-eight coil.

F. Study Questionnaires
None (Y-BOCS to be completed by independent clinician-provider).

G. Study Subjects
To be eligible patients must be aged between 18 yr and 70 yr, have a primary diagnosis of OCD (confirmed by Structured Clinical Interview for DSM-IV), current episode duration of at least a year, have residual OCD symptoms (defined as a total Y-BOCS score of $\geq$16), despite treatment with an adequate trial of a serotonin re-uptake inhibitor (SRI) and cognitive behavior therapy (CBT) [8]. An adequte SRI trial is defined as treatment for at least 12 weeks on the SRI, which meets or exceeds recommended dosage level for OCD [8]. Individuals who cannot tolerate (due to side-effects), medications of this class at the specified dose and duration will also be included. An adequate trial of CBT is 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 will be excluded if they were treatment-refractory

(defined as non-response to clomipramine, at least two selective SRIs (SSRIs) at adequate dose and duration, plus CBT in the last year), diagnosed with severe major depressive disorder (MDD) (defined as Clinical Global Impression (CGI) $\geq$4), exhibited significant acute suicide risk, or had a history of bipolar disorder, of any psychotic disorder, or of substance abuse or dependence within the past year. Patients with neurological disorders, increased risk of seizure, use of proconvulsant medications, implanted devices, metal in the brain, unstable medical conditions, pregnancy, or breast-feeding will be excluded. To avoid confounds on cortex excitability, medications with a known inhibitory effect on brain excitability (e.g. anticonvulsants, benzodiazepines, atypical antipsychotics) will not be allowed. Patients with prior TMS exposure will also be excluded.

H. Recruitment of Subjects

Study subjects will be current patients or new referrals from the Brain Behavior Clinic and the Anxiety Disorders Clinic of New York State Psychiatric Institute/Columbia University. Informed consent will be obtained from patients meeting eligibility criteria as above. An independent psychiatrist at the clinic will evaluate patients and must agree that the patient is suitable for the study and determine that the patient is willing to discuss the study with the research team before any approach is attempted by the investigators. An independent primary care provider must similarly agree that the patient is suitable for the study.

I. Confidentiallty of Study Data

All study subjects will be coded and data collected will be stored in a secure location, accessible only to the investigators

J. Potential Conflict of Interest

None

K. Location of the Study

Brain Behavior Clinic/Division of Therapeutic Brain Stimulation of New York State Psychiatric Institute/Columbia University.

L. Potential Risks

rTMS has been reported to cause seizures in individuals without pre-existing conditions when certain combinations of stimulation frequency and intensity are used, and successful guidelines have been developed to avoid this [18], which are followed in this protocol. In cases in which seizures have been induced, there are no reports that the individuals affected suffered recurrence. Implanted brain stimulators and cochlear implants may be damaged by the magnetic fields and patients with these devices will be excluded as will those with any metal parts in the brain. Subjects may receive sham treatment but will have the option of receiving active treatment at the end of the 4 week study. The subject's condition is not expected to worsen as a result of receiving sham treatment.

M. Potential Benefits

Subjects may or may not benefit with a reduction of OCD symptom severity as a result of participation in this study. Participating in this study will be a benefit to society in determining the utility, if any, of fMRI guided rTMS for treatment-resistant OCD.

N. Alternative Therapies
Experimental: functional neurosurgery/Deep Brain Stimulation. These have the advantage of being invasive and irreversible. Their efficacy is still unclear.

0. Compensation to SubJects
None

P. Costs to SubJects
None

Q. Minors as Research Subjects
None

R. Radiation or Radioactive Substances
None

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