Detailed Protocol:

Title: **Transcranial Magnetic Stimulation (TMS) in Obsessive Compulsive Disorder (OCD): mechanisms and biomarkers.**

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I. BACKGROUND AND SIGNIFICANCE:

Obsessive Compulsive Disorder (OCD)

Obsessive-compulsive disorder (OCD) is a severe, chronic disorder, marked by recurrent, intrusive and distressing thoughts (obsessions) and/or repetitive behaviors (compulsions). OCD among adults in the United States has an estimated lifetime prevalence of 2.3% (Ruscio et al., 2010). Available data from systematic reviews and meta-analyses support cognitive-behavioral therapy (CBT) as efficacious in reducing OCD symptoms (Abramowitz, 1997; Olantunji et al., 2013; Rosa-Alcázar et al., 2008). CBT incorporating exposure and response prevention (ERP) is the psychological treatment of choice for OCD (NICE, 2006). However, approximately 25% of patients who initiate ERP for OCD drop out (Abramowitz et al., 2005). ERP involves gradual prolonged exposure to fear-eliciting stimuli or situations while simultaneously refraining from compulsive behavior. Cognitive therapy (CT), a form of CBT that focuses on modifying dysfunctional beliefs about the presence or significance of intrusive thoughts has also proven effective in the treatment of OCD (Wilhelm et al., 2009). A comparison of effect sizes between CT and ERP suggest no significant differences between variants of CBT for OCD (Abramowitz, 1997; Olantunji et al., 2013; Rosa-Alcázar et al., 2008). Findings from meta-analytic studies of CBT for OCD suggest response rates of 50% to 75% and effect sizes ranging from 0.8 to 1.24 from pre- to post-treatment, but these effects may not be durable (Abramowitz et al., 2005; Jónsson & Hougaard, 2009; NICE, 2006; Olatunji et al., 2013; Ponniah et al., 2013). A recent meta-analysis (Olatunji et al., 2013) found the overall controlled effect size for CBT was significantly larger at post-treatment (Hedge's g = 1.39) compared to follow-up (g = 0.51).

OCD can also be treated with pharmacotherapy, and the preferential efficacy of serotonin reuptake inhibitors (SRI's) led to the so-called serotonin hypothesis (for a review of the neurochemical hypothesis of OCD see Goodman, Grice, Lapidus and Coffey, 2014). An important paradigm is moving psychiatry and the clinical neurosciences from neurochemical models of disease, which originated from clinical observations of pharmacological effects, to a more anatomical and neurophysiological circuit-based understanding of emotion, behavior, cognition and their disorders (Haber & Rauch, 2009). This paradigm shift is important not only because it provides a new understanding of the neuroscientific basis of psychiatric disorders, but also because it leads to the development of novel treatment strategies using neuromodulation of selective

circuits with device-based interventions (George & Aston-Jones, 2010). TMS is one of these treatments, allowing for the directed, noninvasive modulation of neural circuitry with relatively few and benign side effects. The need to develop biomarkers that will help us understand essential pathophysiological processes in order to develop better clinical tools is paramount. Similarly, understanding the mechanism of action of our effective interventions must be a first priority strategy to identify target mechanisms that, when modified, revert pathological states.

Transcranial Magnetic Stimulation

Transcranial Magnetic Stimulation (TMS) is a noninvasive neuromodulation modality that uses powerful and rapidly changing magnetic fields applied over the surface of the skull to generate targeted electrical currents in the brain (Camprodon et al., 2013). TMS has a well-established safety profile and it is able to modulate brain activity without surgery, anesthesia or the generation of a seizure (Rossi et al., 2009). Since its development in the mid-1980s, it has become a widely used tool for neuroscience research and for clinical applications, both diagnostic and therapeutic. In 2008, the FDA approved the use of high frequency repetitive TMS (rTMS) over the left dorsolateral prefrontal cortex (DLPFC) for the treatment of MDD (O'Reardon et al., 2007), and in 2013 the use of deep TMS H-coils for the treatment of MDD was also approved (http://www.accessdata.fda.gov/cdrh_docs/pdf12/k122288.pdf). Additionally, in 2018 the FDA also approved the use of rTMS for the treatment of OCD. TMS has been shown to be a well-tolerated and effective technique that can benefit individuals with MDD through the noninvasive modulation of disease-relevant neural circuits. Clinical and translational research has also shown good safety and efficacy for other disorders, including OCD (Berlim et al., 2013). While different cortical targets have been explored for the treatment of OCD, inhibiting the pre-Supplemental Motor Area (pre-SMA) with low frequency (1Hz) rTMS has shown the best results so far (Mantovani et al., 2010).

Nevertheless, the literature on TMS for OCD remains noisy and the clinical outcomes, while promising, need improvement. An important source for this variability is the lack of individualized methods to identify and target the appropriate cortical nodes for stimulation. Our study will address this by using individual fMRI maps to identify the target and neuronavigation technology to precisely and consistently inhibit it with TMS. Another critical variable driving these inconsistencies in the field is the lack of mechanistic understanding of the effects of TMS in OCD. A priori hypotheses about disease mechanisms have driven the choices of targets of stimulations in the published clinical trials (based on a fairly robust understanding of the circuitry involved in the pathophysiology of OCD), but most studies limited themselves to measuring clinical outcomes. While this pragmatic approach is valuable, it leaves too many open questions and requires too many assumptions. Our study will innovate by proposing a translational systems neuroscience approach to understanding not only the safety and efficacy of TMS in patients with OCD, but also the physiological and anatomical changes driving (or resisting) response and remission.

II. Specific Aims

In this proposal we will apply functional neuroimaging-guided inhibitory rTMS to the pre-SMA in patients with OCD, integrating neuroimaging, behavioral and clinical research tools in a randomized controlled clinical trial. We will assess the safety and efficacy of this novel individualized strategy, study the mechanism of action at the circuit-level, and identify biomarkers and predictors of response.

Aim 1: To assess the efficacy of fMRI-guided 1HZ rTMS over the pre-SMA:

We hypothesize that patients randomized to 6 weeks of daily 1Hz rTMS will have a greater reduction in OCD symptom severity than patients randomized to identical placebo stimulation.

Aim 2: To identify the mechanisms of action of TMS at the circuit-level:

Hypothesis 2.1: We hypothesize that decreased connectivity between the pre-SMA, the Orbito-Frontal Cortex (OFC) and dorsal Anterior Cingulate Cortex (dACC) will correlate with clinical improvement.

Hypothesis 2.2: We hypothesize that TMS would improve fear extinction retention from pre- to post-treatment, and increase functional activation of the fear extinction network during extinction recall. The extinction network includes the ventromedial prefrontal cortex (vmPFC), dACC, and hippocampus.

Aim 3: To identify biomarkers and predictors of treatment response:

Hypothesis 3.1: We hypothesize that pathological hyperconnectivity between the pre-SMA, the Orbito-Frontal Cortex (OFC) and dorsal Anterior Cingulate Cortex (dACC) will correlate with OCD symptom severity in the pre-TMS scans.

Hypothesis 3.2: We hypothesize that (a) pathological hyperconnectivity between the pre-SMA the Orbito-Frontal Cortex (OFC) and dorsal Anterior Cingulate Cortex (dACC) and (b) early reduction of this pattern after week 1 of TMS will predict positive clinical outcomes after TMS.

III. SUBJECT SELECTION

There will be two different groups of patients with OCD in this study: one will receive active stimulation and one sham stimulation (i.e. placebo). We will recruit as many patients as are needed in order to obtain 20 completers per group (i.e. 40 patients in total). We expect an early termination rate of 30%, and we will anticipate the need to recruit and consent a total of 58 patients overall.

Inclusion Criteria:

1) 18-65 years of age.
2) Proficient in English.
3) A diagnosis of primary OCD (as determined by SCID).
4) Yale-Brown Obsessive Compulsive Scale total score ≥ 16.
5) Normal (or corrected) vision.
6) Stable OCD medication regimen or OCD medication free for ≥ 12 weeks prior to study.

7) Able to give informed consent.

Exclusion Criteria:

1) Current or history of neurologic or psychiatric disease (e.g., mental retardation, dementia, brain damage, or other cognitive impairment) that would interfere with ability to engage in TMS
2) Psychopathology not appropriate for the treatment (e.g., manic episode or psychosis)
3) Substance abuse or dependence that is current or within the last six months or use of an illicit drug that is not prescribed, as indicated by a urine drug screen and/or clinical inference.
4) Use of anticonvulsants within 2 weeks prior to study (to be ruled out by a urine drug screen.
5) Use of Tricyclic Antidepressants (e.g. Clomipramine).
6) Use of psychotropic medication is allowed (except for the limitations specified on use of OCD regimens, anticonvulsants, and tricyclic antidepressants).
7) Documented resistance to 4 or more valid pharmacological trials of 2 or more different medication classes (e.g. SSRIs and TCAs).
8) Previous exposure to TMS.
9) Major/chronic medical conditions.
10) History of head injury resulting in prolonged loss of consciousness and/or neurological sequelae.
11) Prior neurosurgical procedure.
12) Metal in the body **that is ferromagnetic**, metal injury to the eyes
13) History of seizures.
14) Implanted pacemaker, medication pump, vagal stimulator, deep brain stimulator, TENS unit, or ventriculo-peritoneal shunt
15) Pregnancy; breastfeeding or nursing; for women of childbearing a pregnancy test (to be ruled out by urine β-HCG) will be conducted prior to study.
16) Currently in Cognitive Behavioral Therapy (CBT).
17) Diagnosis of primary sleep disorder such as primary insomnia, narcolepsy, sleep apnea, shift work sleep disorder and others. Sleep disorders such as insomnia or hypersomnia that are secondary to depression or OCD are permitted.
18) Current clinically significant suicidality

Recruitment:

OCD patients will be recruited from the Obsessive-Compulsive Disorder Clinic at MGH, as well as elsewhere in the hospital or in its clinics. Persons inquiring to other hospital research and clinical staff about OCD research opportunities may also be included. Subjects may be recruited from persons who have listed themselves on the RSVP for Health Recruitment Registry or ResearchMatch.org as volunteers to participate in OCD research. We may also use paid advertising on the internet, television, and Boston MBTA in order to reach out to more potential subjects. Efforts will be made to attain a mix of study participants, in terms of gender and racial/ethnic representation, that is reflective of the respective populations under study. Specifically, with regard to gender, it is anticipated that half of the subjects will be male, and half will be female. Similarly, it is anticipated that minority representation in the study cohorts will be

reflective of the respective populations under study. In the event that early recruitment efforts yield under-representation of any of the above groups, active outreach will be initiated (through advertisement) in an effort to achieve the above goals.

IV. SUBJECT ENROLLMENT

The formal recruitment will take place at the first study visit to MGH. Necessary data will be gathered for the subject identification and remuneration, including date of birth, gender, years of education, address, telephone number, and social security number. Informed consent will be obtained by doctoral level licensed clinician study-staff or study staff that are doctoral candidates under the supervision of doctoral-level licensed clinicians prior to participation in the study using the e-consent module in REDCap™ and IRB-approved consent form. If the participant agrees to participate, the consent form will be signed electronically by the research participant and the individual obtaining consent. Each participant will be emailed a copy of the signed and dated consent form.

V. STUDY PROCEDURES

This study will have 2 phases: phase 1 will be a randomized, double-blinded, placebo-control trial, and phase 2 will be an open-label trial in which all patients who did not remit after completion of phase I (regardless of treatment group), will be invited to receive an additional 6 weeks of real TMS. Remitters will be defined as those subjects who have a week six Y-BOCS score of 12 or less.

1. Subjects Assessment

All candidates for this project will undergo a comprehensive clinical evaluation including a clinical interview to establish relevant psychiatric, medical and neurological history and a structured clinical interview (Structured Clinical Interview for DSM-IV Axis I Disorders; SCID-I) to confirm psychiatric diagnoses, the Edinburgh Handedness Inventory – Short Form (EHI) to establish handedness, the Beck Depression Inventory (BDI), HAM-D, and PHQ-9 to quantify depressive symptoms, the Beck Anxiety Inventory (BAI) to quantify general anxiety symptoms, the Speilberger State Trait Anxiety Inventory (STAI) to quantify trait vs. state aspects of anxiety, the Anxiety Sensitivity Index (ASI) to quantify anxiety sensitivity, and a covid-19 impact scale to assess the effect of the coronavirus pandemic in the past week. The Yale Brown Obsessive-Compulsive Scale (YBOCS), Obsessive-Compulsive Beliefs Questionnaire-44 (OBQ), the Compulsive Behaviors Form (CBF), and Obsessive-Compulsive Inventory (OCI-R) will be used to measure OCD symptoms and severity. The Clinical Global Impressions (CGI) rating scale will be used as an additional measurement of clinical change from baseline (see detailed description below). In addition, the Rey-Osterrieth Complex Figure Test and the Stroop and Wisconsin Card Sorting tasks will be conducted to assess relevant aspects of executive function and selective attention (see detailed description below). The initial evaluation of all subjects will be audio recorded for inter-rater reliability, and therapist supervision purposes. The digital recordings will contain participant ID numbers but not names or other identifying information. Digital recordings will be rated and simultaneously entered in the REDCap data management system for

analysis. The digital recordings will be kept by the research team in a password-protected file and destroyed after completion of the study. When possible, assessments will be used from previous studies in the OCD program (to which participants will consent).

After the initial thorough baseline assessment, patients will be assessed longitudinally through the course of the study at weeks 2, 4, 6 and 3 months after the last TMS session. These assessments will be shorter and will include the following measures: YBOCS, OBQ, OCI-R, BDI, HAM-D, PHQ-9, and covid-19 impact scale. The Rey-Osterrieth Complex Figure Test and the Wisconsin Card Sorting and Stroop tasks will also be conducted at week 6.

As of July 8th, 2020, a majority of the clinical assessment procedures will take place virtually using Healthcare Secure Zoom™, including the SCID-I, Y-BOCS, EHI, HAM-D, CGI, and CBF. Likewise, the following self-report instruments will be administered remotely via REDCap™: the demographics form, OCIR, ASI, OBQ, PHQ-9, CGI – Patient Version, and covid-19 impact scale. Additionally, subjects will be screened for covid-19 symptoms before attending in-person clinical study visits (baseline, week 6, and 3-month follow-up for phases 1 and 2) by completing a covid-19 symptom attestation form via REDCap™. Administration of the ROCF, WCST, Stroop, Goal-Oriented versus Habit-Driven Behaviors Task, BDI, BAI, STAI, and urine drug screen, however, will take place **in-person** at the MGH-main campus (Simches).

Clinical Global Impressions (CGI) scale

This global rating scale, which ranges from 1 (very much improved) to 7 (very much worse) (Rush et al, 2008), is commonly used in pharmacotherapy trials. Subjects and will complete a CGI for OCD symptoms (CGI-OCD) and for overall symptoms (CGI-global) at each assessment, captured in the CGI-Patient form. The independent evaluator will complete the CGI-OCD and CGI-global at each assessment, captured in the CGI-Clinician form. Additionally, the independent evaluator will complete a CGI-Severity (CGI-S) at baseline.

Rey-Osterrieth Complex Figure Test

The Rey-Osterrieth Complex Figure Test (ROCF; Rey, 1941 and Osterrieth, 1944) evaluates visuospatial ability, executive functioning, and memory. Subjects reproduce a complicated line drawing by copy and then by memory. Participants will be asked to copy the figure with the stimulus card present (copy trial), and later to reproduce the figure from memory at two separate time points (3 min delay and 30 min delay) followed by a recognition portion. We will score *organization* (executive function) and *accuracy* (memory) using the Savage (Savage et al., 1999) and Denman (Denman, 1984) systems, respectively. The ROCF is sensitive to change (Buhlmann et al., 2006; Park et al., 2006; Kang et al., 2003; Kuelz et al., 2006).

The Wisconsin Card Sorting Task

The Wisconsin Card Sorting Test (WCST; Grant & Berg, 1981) is a measure of executive function and strategic planning, particularly with the ability of an individual to use feedback from the environment to shift individual cognitive sets and experience goal-

directed behavior. During this 10-15 minutes test, four stimulus cards incorporating color, form, and number are presented to a subject. The subject must sort the cards according to different rules or principles and be able to change their approach throughout the test administration.

The Stroop Task

The Stroop Task (Stroop, 1935) employs both controlled (color naming) and automatic (reading) processes. Participants are asked to complete the approximately five-minute task by naming the color ink of a word while ignoring the meaning of the word. In the classic Stroop Task, all words are the names of colors. The difference in time between naming the ink of a different color-word (e.g. the word 'red' is written in blue ink) versus naming the ink of a same color-word (e.g. the word 'red' is written in red ink) demonstrates the interference of automatic reading processes on controlled color naming processes. A larger Stroop interference represents difficulty with selective attention processes, processing speed, and response inhibition (e.g. Ben-David, Nguyen, van Lieshout, 2011).

Goal-Oriented versus Habit-Driven Behaviors Task

This 20-minute computer-administered task measures whether behaviors are planned and purposeful (e.g., goal-oriented) or automatic (e.g., habit-driven). In the two-step task, participants first learn to associate certain behaviors (i.e., choosing one image of a fractal over another) with rewards. Then, the rewards are devalued, and we assess whether the participants' choices change in response to the devaluation. This task has been piloted and tested with healthy individuals (Gillan et al., 2015), as well as individuals with OCD (Gillan et al., in preparation). In order to incentivize participants during the task, a small monetary award is promised based on participation (approximately $1, no more than $2 per administration).

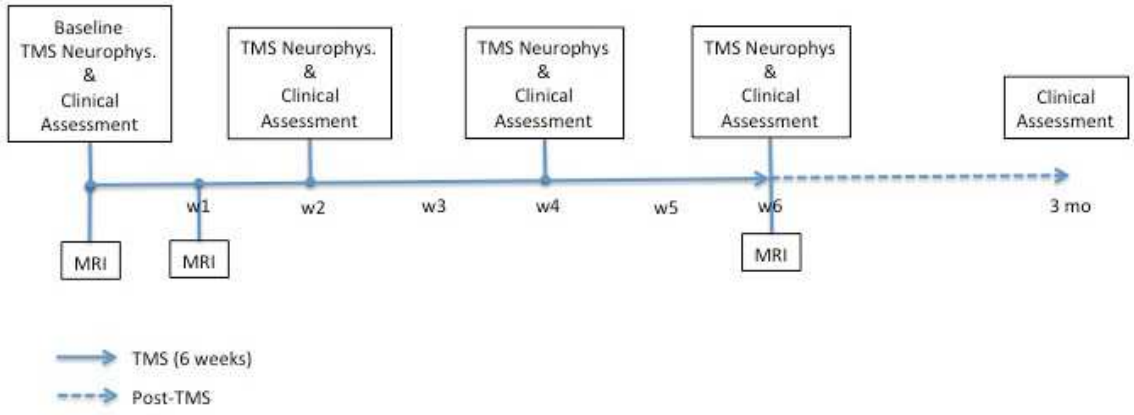
2. Patient randomization and clinical trial design

2.1 Phase 1: Randomized placebo controlled

Patients will be randomized to receive real or sham rTMS using the variable-sized permuted blocks randomization algorithm (with a maximum block size of 4), with randomization stratified by symptom severity (Y-BOCS total score ≤31 vs. >31) and age (≤ 34 vs. >34 years at entry), to ensure balance in these factors across arms in this small study. Randomizations will be conducted in SAS using procedures outlined by Efird (2011) [Efird, J. Blocked Randomization with Randomly Selected Block Sizes. *Int. J. Environ. Res. Public Health., 8, 15-20*]. The randomization codes generated by our statistician/data manager for each of the 4 strata will be communicated to the study coordinator at the time of randomization (i.e. at the patient's baseline visit), based on the stratum to which the patient belongs. Patients will be blinded to their treatment arm. Patients will receive 6 weeks of daily treatments Monday through Friday (not on weekends). There will be 3 MRI sessions that will take place (i) within 2 weeks prior to the first TMS session, (ii) at the end of week 1 of treatment and (iii) within 2 weeks after the last TMS session. Longitudinal clinical assessments will take place throughout the course of study at the end weeks 2, 4 and 6 of TMS, in addition to a last assessment 3 months after TMS. Physiological assessments to measure cortical excitability and

plasticity in the motor cortex using single and paired-pulse TMS will also take place the 1st day of treatment and at the end of weeks 2, 4 and 6 of TMS.

Figure 1: Clinical Trial Design for Phase 1



2.2 Phase 2: Open label TMS

Patients who do not remit following the double-blinded phase of the study will be given the option to enter an open-label phase 2 and receive an additional 6 weeks of real rTMS (regardless of whether they received real or sham TMS in phase 1). Phase 2, like phase 1, will also include an MRI session at the end of week 1 and at the end of week 6, clinical assessment at weeks 2, 4 and 6, and TMS neurophysiological assessments at the end of weeks 2, 4 and 6.

3. Transcranial Magnetic Stimulation

We will use a MagVenture MagPro X100 with MagOption stimulator and two dynamic cooled butterfly coils: one real and one sham (MagVenture, Denmark) navigated with an infrared TMS Neuronavigation Research Premium system (Localite, Germany) to administer the TMS.

We will start by measuring the patient´s motor threshold (MT), which is a measure of cortical excitability used to standardize the intensity of stimulation across subjects. To do this, the TMS coil is placed over the hand representation of the primary motor cortex (M1) in a rostro-medial 45º angle. Single pulses are applied with an interpulse interval (IPI) of at least 7 seconds, to prevent additive neuromodulatory effects. When pulses are applied at suprathreshold intensities, a volley of activity travels through the pyramidal motor pathways and leads to the contraction of the contralateral hand muscle. The intensity of stimulation is sequentially reduced until we reach a point when fewer than 50% of the pulses (usually <3 out of 6) lead to a muscle contraction (identified by visual inspection or neurophysiological motor evoked potentials). The first TMS intensity that is unable to elicit a muscle contraction more than 3 out of 6 pulses is considered the motor threshold, and usually expressed as a percentage of the maximum stimulator output.

Once the MT is determined, we will define our target of stimulation using the fMRI data obtained and analyzed days prior to the first TMS session. Using the Localite TMS neuronavigation system we will corregister the patient´s head to their MRI, and place the TMS coil over the scalp position that corresponds to the cortical target.

At this point, the treatment session can begin. We will use an inhibitory protocol of 1Hz stimulation at 110% of the motor threshold intensity and a total of 1800 pulses per session. This will have a duration of 30 min. This protocol complies with published safety guidelines (Rossi et al., 2009). Sessions will occur daily Monday through Friday over 6 weeks.

Sham TMS will use the exact same procedure with a sham coil, which is designed to induce the same nonspecific sensory effects of TMS (auditory and somatosensory activation) without inducing the neuromodulatory magnetic fields.

4. Transcranial Magnetic Stimulation neurophysiological measures

The history of TMS has been closely linked to motor neurophysiology; the first applications were indeed geared towards the study of cortical physiology in humans. Both single and paired-pulse protocols have been established to study cortical excitability and plasticity (both intracortical inhibition and facilitation). These protocols lead to robust effects in healthy controls and are used regularly in clinical practice for diagnostic applications in neurological populations (Groppa et al., 2012). Pharmacological studies have been conducted to understand the neurochemical dynamics driving these effects (Paulus et al., 2008). Like all other TMS applications, these measures are noninvasive, and their safety has been well established (Rossi et al., 2009).

OCD results from the deficits in cortical inhibition and excessive excitatory states within specific brain networks. TMS measures of excitability, inhibition and facilitation have been shown to be abnormal in patients with OCD, to reflect clinical severity and to respond to treatment (Mantovani et al., 2013). We will use the following measures to obtain neurophysiological markers of severity and response, in addition to the other neuroimaging and behavioral measures described in this protocol.

The following 5 measures will be assessed:

- Resting Motor Threshold
- Active Motor Threshold
- Cortical Silent Period
- Short-Interval Cortical Inhibition (SICI).
- Intracortical Facilitation (ICF)

4.1 Motor threshold (resting and active)

The resting motor threshold (RMT)/active motor threshold (AMT) are defined as the minimum TMS intensity needed to induce a muscle contraction or motor evoked potential larger than 50 **m**V in at least 50% of the trials, typically 3 of 6 or 5 of 10 TMS pulses (Groppa et al., 2012). We will reassess the motor threshold following the same procedure used on day 1 of treatment and described above. The resting motor threshold is measured with the muscle of study at rest. The active motor threshold is measured with a voluntary contraction of the muscle. Motor thresholds are measures of cortical excitability and reflect the activity of neuronal membranes and the excitability of corticocortical axons, synapses and their sodium channels (NMDA-associated transmission and GABAergic mechanisms are less involved) (Ziemann, 2004).

4.2 Cortical silent period

The cortical silent period CSP is defined as a reduction of the ongoing tonic muscle activity, lasting up to 300 ms after the contralateral TMS pulse to the primary motor cortex. It can be subdivided into the contralateral (CSP) and the ipsilateral (ISP) cortical silent period. Its length can be defined as the duration from the beginning of an MEP to

the re-emergence of baseline EMG-activity. The first 50 ms represent spinal mechanisms of inhibition, while later inhibition is influenced by cortical networks (Chen et al., 1999). This inhibitory phenomenon is thought to be driven primarily by GABAB-receptors (Ziemann, 2004). The ISP represents neuronal activity on the muscle ipsilateral to the site of stimulation and, therefore, measures cortical phenomena contralateral to the site of stimulation and the function of the corpus callosum connecting both hemispheres (Meyer et al., 1995).

4.3 Short-interval intracortical inhibition (SICI)

The application of a first stimulus below motor threshold followed by a second stimulus above motor threshold, with a short interstimulus interval (ISI) of 1-5 ms, results in a physiological reduction of cortical excitability (short-interval intracortical inhibition (SICI)) (Groppa et al., 2012). This parameter reflects inhibitory effects mediated mainly by GABAA-receptors, as well as dopamine and acetylcholine (Ziemann, 2004).

4.4 Intracortical facilitation (ICF)

The same paired-pulse configuration used in SICI but applied at longer ISIs of 10-17 ms or longer results in increased excitability (Groppa et al., 2012). This intracortical facilitation (ICF) seems to be mediated principally by glutamatergic neurotransmission, although the underlying physiology is less clear in this case (Ziemann, 2004).

5. Magnetic Resonance Imaging

MRI sessions will include both structural and functional imaging. MRI scanning will be conducted on a 3T scanner equipped with multichannel receivers. Protocols have been developed and validated at the Martinos Center for Biomedical Imaging. Resting state MRI sessions will be obtained while participants focus on a fixation cross (functional scans) or have their eyes closed (structural scans). Task fMRI scans (see fear conditioning below) will be performed while subjects have their eyes open and receive visual, auditory and somatosensory stimulation via integrated MRI-compatible audiovisual equipment. Patient will be required to respond using an MRI-compatible fiber-optic response-box.

5.1 Multi-Source Interference Task

The Multi-Source Interference Task (MSIT) is a cognitive paradigm that was designed to reliably identify the cingulo-frontal-parietal cognitive/attention network (CFP network) within individual subjects (Bush et al., 2006). Among other relevant brain regions, the pre-SMA and dorsal anterior cingulate cortex are activated in this 10-15 task when performed inside of the scanner. We will use this fMRI cognitive paradigm to identify our target of stimulation on an individual-subject basis.

Briefly, the MSIT presents a string of 3 numbers to subjects, which can be different combinations of 0,1,2,3 in which 2 numbers are the same and one is different (e.g. 100, 323, 221). Subjects are asked to identify what number is different by pressing one of 3 buttons available in the response box. Some trials will be congruent (e.g. 100) and some incongruent (010), depending on the position of the number that is different. Analyzing the brain response to these congruent and incongruent trials has been shown to robustly

identify these brain networks and regions at the individual level in healthy and patient populations (Bush et al., 2006).

5.2 Fear Conditioning:

All subjects randomized prior to February 27th, 2018 will undergo a 2-day fear conditioning protocol. The experiments will be carried out in a 3T scanner. In accordance with previously published procedures (Orr et al., 2000), prior to the initiation of the experiment, recording electrodes will be attached to the palm of the subject's non-dominant hand to measure SCR, and stimulating electrodes will be connected to two fingers of the subject's dominant hand through which the electric shock will be delivered. SCR will be measured through 9-mm (sensor diameter) Sensor Medics Ag/AgCl electrodes (safe for use in the magnet environment).

Subjects will view two rooms presented on a monitor, both of which differ in color and content (e.g., an office and a kitchen). The conditioned stimuli (CSs) will be different cues in the room. The CS+ and the US will only be presented in one context (conditioning context; CX+). The other context will be used for extinction training (CX-). Neither CS+ presented in the context of the CX-, nor a CS- presented in either context, will ever be paired with the US. In one of the four possible CS-CX combinations, for example, the office will serve as the dangerous context, in which the subjects will receive electric currents only when the yellow light is on, whereas the kitchen will serve as the safe context, in which no electric currents will be delivered. On day 2, subjects are placed back in the magnet and will be presented with additional extinction trials to CSs in pseudorandomorder.

As of February 27th, 2018, the fear conditioning paradigm will no longer be administered to participants in this study. All fear conditioning data collected prior to February 27th will be analyzed.

VI. BIOSTATISTICAL ANALYSIS

Analysis of Aim 1: To compare change in OCD symptom severity by treatment group, we will utilize a mixed effects linear regression model with Y-BOCS total score as the outcome, a random effect for time (study week), a fixed effect for group (rTMS versus placebo stimulation), and the interaction between time and treatment group (which is the covariate of interest). We will also control for potential confounding by any covariates that are significantly imbalanced between the treatment groups.

Analysis of Aim 2.1: Specification of the analyses examining whether decreased connectivity between the pre-SMA, the Orbito-Frontal Cortex (OFC) and dorsal Anterior Cingulate Cortex (dACC) correlates with clinical improvement can be found below, in the MRI data section - Resting state Connectivity Analysis.

Analysis of Aim 2.2: Specification of the analyses examining whether TMS improves fear extinction retention from pre- to post-treatment, and whether increased functional activation of the fear extinction network (vmPFC, dACC, and hippocampus) during extinction recall can be found below, in the MRI data section - Fear Extinction.

Analysis of Aim 3: To identify biomarkers and predictors of treatment response, we will us linear regression analysis to examine predictors of clinical improvement. The outcome will be the post-treatment Y-BOCS score, the covariate of interest will be each ROI (examined in separate models to begin with, to avoid issues of collinearity), and we will control for the pre-treatment Y-BOCS score. Univariately significant predictors will then be entered into a multivariate linear regression model using step-wise selection (alpha=0.10 to enter, alpha=0.05 to stay).

TMS neurophysiology

Numeric values for each of our 5 physiological measures will be obtained at each of the established times (baseline, week 2, week 4, week 6). A general linear model will be used to assess the difference in longitudinal progression of these measures between the active and placebo group.

MRI data

Fear Extinction

During the extinction training on day 1, the principal contrast for the fMRI data will be CS+ vs. CS-, to establish the substrates of extinction learning. During extinction recall on day 2, the principal contrast will be CS+1 vs. CS+2. Analyses of SCR will test for group x condition interactions for OCD vs. HC with respect to CS2 vs. CS1. With respect to the fMRI data, the initial analysis will involve assessing for a main effect of condition (across both groups), by comparing CS1 vs. CS2 during extinction learning and recall. Finally**,** voxel-wise analyses will also be performed to identify specific loci of significant group x condition interactions (OCD, HC x CS2, CS1) within designated prefrontal search territories of interest.

With respect to SCR analyses, the SCR for each CS will be calculated by subtracting the mean level for the 2 s immediately preceding CS onset from the highest value among those recorded during the 10-s CS interval. Values will be subjected to repeated measures ANOVA to test hypotheses regarding both within-group and between-group differences at an alpha of $p<0.05$. Significant interactions will be followed-up with t-tests where indicated. Change in clinical symptoms from pre- to post- treatment, such as the change in YBOCS scores will be correlated with improved extinction retention index from pre- to post-treatment. Voxel-wise regression using change in YBOCS scores will be conducted against BOLD responses during extinction learning and recall to identify changes in functional activation of brain regions associated with change in clinical symptoms.

Multi-Source Interference Task

Standard task-based neuroimaging analyses procedures will be used to analyze the brain activity resulting from patients performing the MSIT in the scanner, including pre-processing and statistical parametric mapping using general linear models.

Resting state Connectivity Analysis

Functional connectivity analysis will employ a regional approach based on Biswal (Biswal, Yetkin, Haughton, & Hyde, 1995) and extended in Fox (Fox et al., 2005) and Vincent (Vincent et al., 2006). This approach has been previously used by our group and

others to study the medial temporal lobe memory system (Kahn, Andrews-Hanna, Vincent, Snyder, & Buckner, 2008), the frontal parietal control system involved in executive function (Vincent et al., 2006), and the default network (Buckner & Vincent, 2007), as well as initial explorations in aging (Andrews-Hanna et al., 2007). Following standard preprocessing, several additional steps are employed to condition the fMRI data for analysis of voxel-based correlations (described in Vincent 2006). Temporal band-pass filtering will remove frequencies greater than 0.08Hz. Several sources of spurious variance along with their temporal derivatives will then removed from the data through linear regression: (i) six parameters obtained by rigid body correction of head motion, (ii) the whole-brain signal averaged over a fixed region in atlas space, and (iii) the signal from a ventricular region of interest and a region centered in the white matter. In this manner, variance unlikely to be involved in spatially specific regional correlations is removed from the data. The global (whole brain) signal may correlate with respiration-induced fMRI signal fluctuations or result from global fluctuations in neuronal activity. Removing signals correlated with ventricles and white matter is an additional means of reducing non-neuronal contributions to BOLD correlations (Fox et al., 2005). Following preparation, maps of functional connectivity are obtained by plotting the correlation strength at each voxel to the time course of a seed region. Between-region correlations are obtained by extracting the time courses for multiple regions and computing the correlation coefficient between regions pairs. ANCOVA analysis will be performed covarying for the clinical and behavioral measures.

Cortical reconstruction and volumetric analysis

Cortical reconstruction and volumetric segmentation will be performed with the Freesurfer image analysis suite, which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/). The technical details of these procedures are described in prior publications (Dale et al., 1999; Dale and Sereno, 1993; Fischl and Dale, 2000; Fischl et al., 2001; Fischl et al., 2002; Fischl et al., 2004a; Fischl et al., 1999a; Fischl et al., 1999b; Fischl et al., 2004b; Han et al., 2006; Jovicich et al., 2006; Segonne et al., 2004)). Briefly, this processing includes motion correction and averaging (Reuter et al. 2010) of multiple volumetric T1 weighted images (when more than one is available), removal of non-brain tissue using a hybrid watershed/surface deformation procedure (Segonne et al., 2004), automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures (including hippocampus, amygdala, caudate, putamen, ventricles)(Fischl et al., 2002; Fischl et al., 2004a) intensity normalization (Sled et al., 1998), tessellation of the gray matter white matter boundary, automated topology correction (Fischl et al., 2001; Segonne et al., 2007), and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class (Dale et al., 1999; Dale and Sereno, 1993; Fischl and Dale, 2000). Once the cortical models are complete, a number of deformable procedures can be performed for further data processing and analysis including surface inflation (Fischl et al., 1999a), registration to a spherical atlas which utilized individual cortical folding patterns to match cortical geometry across subjects (Fischl et al., 1999b), parcellation of the cerebral cortex into units based on gyral and sulcal structure (Desikan et al., 2006; Fischl et al., 2004b), and creation of a variety of

surface based data including maps of curvature and sulcal depth. This method uses both intensity and continuity information from the entire three dimensional MR volume in segmentation and deformation procedures to produce representations of cortical thickness, calculated as the closest distance from the gray/white boundary to the gray/CSF boundary at each vertex on the tessellated surface (Fischl and Dale, 2000). The maps are created using spatial intensity gradients across tissue classes and are therefore not simply reliant on absolute signal intensity. The maps produced are not restricted to the voxel resolution of the original data thus are capable of detecting submillimeter differences between groups. Procedures for the measurement of cortical thickness have been validated against histological analysis (Rosas et al., 2002) and manual measurements (Kuperberg et al., 2003; Salat et al., 2004). Freesurfer morphometric procedures have been demonstrated to show good test-retest reliability across scanner manufacturers and across field strengths (Han et al., 2006; Reuter et al., 2012).

To extract reliable volume and thickness estimates, images will be automatically processed with the longitudinal stream in FreeSurfer (Reuter et al., 2012). Specifically an unbiased within-subject template space and image (Reuter and Fischl, 2011) is created using robust, inverse consistent registration (Reuter et al., 2010). Several processing steps, such as skull stripping, Talairach transforms, atlas registration as well as spherical surface maps and parcellations are then initialized with common information from the within-subject template, significantly increasing reliability and statistical power (Reuter et al., 2012).

Diffusion MRI and Tractography

Diffusion images will be corrected for motion and eddy currents, using affine registration to a b0 reference volume, by using FSL-based software. A tensor model will then be fitted to each voxel, generating different diffusivity maps. Finally, we will use TBSS (Smith et al., 2006) to perform voxel-wise statistical analyses for relevant diffusivity measures: functional anisotropy (FA), and mean axial and radial diffusivity (MD, AD, RD).

Two-tensor whole brain tractography will be implemented for tract analysis. This form of tractography involves a recursive process that both fits local parameters at each step and propagates the fiber in the most stable direction, allowing simultaneous tractography and model estimation. This model also uses a covariance matrix to measure confidence, which reduces false positives, and implements two eigenvalues per voxel, which improves resolution of and accounts for branching and crossing fibers. Whole-brain tractography will be used to best account for all potential tracts among the ROIs, which may be otherwise limited in solely ROI-based tractography (Yang et al., 2014).

Power for the Primary Aim

For the primary analysis comparing change in Y-BOCS total score by treatment group, with 20 patients per group and a two-sided alpha of 0.05, we will have 90% power to detect an effect size of 1.06. Due to the novelty of our approach, no comparable data exist to inform the power calculation. However, Mantovani et al. (2010) examined change in Y-BOCS total score among 18 OCD patients (completers) randomized to 4 weeks of similar rTMS or sham treatment. Based on their reported F-statistic comparing change in Y-BOCS total score after 4 weeks of treatment, their observed effect size,

expressed as Cohen's *d* (Thalheimer & Cook, 2002), was 1.8. Based on these results, we believe that our study will be adequately powered to detect anticipated effect sizes.

VII. RISKS AND DISCOMFORTS

Participation in this study poses minimal foreseeable risks. Patients may experience psychological discomfort when discussing psychiatric history and/or current psychiatric symptoms or side effects. Answering detailed questionnaires may also create some inconvenience for subjects. Confidentiality of all subjects will be protected per institutional and federal requirements.

Repetitive TMS at high frequencies has the rare potential to induce a seizure even in healthy individuals (~ 8 reported cases worldwide since the invention of TMS in 1985), but the risk for seizure can be effectively managed by using appropriate subject selection criteria and by keeping the TMS parameters within the safety parameters of the international safety consensus (Rossi et al., 2009). In addition, this study proposes the use of low-frequency rTMS, which has a cortical inhibitory effect, and single-pulse TMS for physiological assessments, which does not have carry-over cumulative effects. To protect subjects from the risk of a seizure, this study strictly adheres to the international safety consensus and will exclude subjects at increased risk for seizures (Rossi et al., 2009). In the unlikely event that a suspected seizure would occur, the seizure stops as soon as TMS is stopped, and the TMS clinical service safety plan is activated, including transfer of the subject with ambulance to MGH ER for a medical and neurological evaluation. No one has ever developed epilepsy as a consequence of TMS. There are no known or foreseeable long-term risks associated with TMS. TMS is not uncomfortable but the subject may feel twitching of the scalp muscles during stimulation. It is possible that the subject may feel headache after the TMS measurement that is caused by keeping the head in the same position for a lengthy period of time and/or by stimulation of the scalp muscles and nerves by the TMS pulses. The headache, if present, is typically mild, disappears soon and, if needed, can be treated by mild over-the-counter analgesics that are available to study participants.

The risks of the MRI examination are essentially identical to those of a standard, clinically employed, anatomical MRI study. There is no ionizing radiation. The technique is non-invasive and we will not administer any contrast agent. A certain percentage of people cannot tolerate the MRI environment, usually due to claustrophobia. We will monitor subjects and we will be in constant auditory contact with the subjects. The study can be immediately stopped at the subject's request. The MR machine will make a number of sounds; the intensity of these sounds is not harmful to one's hearing if one wears a headphone or earplugs which will be routinely provided to our subjects. Contraindications to participating in MRI studies exist for those subjects who have metallic or other electronic devices implanted such as pacemakers, electronic implants, shrapnel in the eye, certain intracranial aneurysm clips, etc. All subjects will fill out a detailed questionnaire with regard to any implanted metal or devices or any shrapnel injuries. These contraindications constitute reasons for exclusion from the present study.

The safety of our fear conditioning paradigm has been established and approved in multiple IRB-approved research protocols world-wide and at MGH. The electrical shock that will be applied to the fingers during the fear conditioning paradigm is uncomfortable but not painful. The finger stimulator is powered by a 9V battery and has been approved by Partners Biomedical Engineers.

1. PROTECTION AGAINST RISK

All potential subjects will be screened for TMS and MRI risk factors prior to study enrollment. If the potential subject cannot rule out the possibility of pregnancy, a pregnancy test will be conducted prior to study enrollment. All enrolled subjects will again be screened just before undergoing MRI. These screening procedures should exclude subjects with foreseeable risks. All subjects will be monitored continuously by research investigators during MRI sessions. Subjects will be able to communicate with research investigators throughout all experimental sessions, including during MRI scans via a 2-way microphone. All subjects will wear earplugs during MRI and TMS. Earplugs will reduce the transmission of noises of the TMS coils and MRI scanner (e.g., buzzing, beeping) to a comfortable and safe level. If a subject experiences any discomfort that cannot be alleviated by the research investigators, the experimental session will be terminated.

VIII. POTENTIAL BENEFITS

Patient may benefit from this intervention by improving their symptoms of OCD. Patient randomized to the placebo arm will be given the option to enter an open-label phase when they will receive an additional 6-weeks of active rTMS.

IX. MONITORING AND QUALITY ASSURANCE

All study procedures will be in accordance with the MGH subcommittee on Human Studies. The principal investigator will oversee the collection, maintenance, and analysis of the data. Research Affairs will be contacted immediately in the case of unexpected adverse events.

A Data and Safety Monitoring Board will review the progress of the study annually, discuss any safety concerns that arise, and make recommendations to improve safety procedures if indicated. No member of the DSMB is otherwise involved with the study. Board members will consist of **Mark Vangel, Ph.D.,** Assistant Professor of Radiology, Harvard Medical School; **Scott Rauch, MD**, President and Psychiatrist in Chief, McLean Hospital; and **Heather Urry, Ph.D**., Associate Professor of Psychology, Tufts University. **Dr. Vangel** was chosen for his expertise in statistical methods of neuroimaging analysis, and because, through his work as a biostatistician at the MGH and MIT General Clinical Research Centers, he has extensive experience in issues related to safe and ethical practices in biomedical research with human subjects. **Dr. Rauch** was chosen for the DSMB because he has conducted extensive research on neuroimaging,

neurobiology, and neuromodulation of mood and anxiety disorders using modern technology, including brain stimulation and neurosurgery. **Dr. Urry** was chosen for the DSMB because she has extensive experience with fMRI and peripheral psychophysiology research. The DSMB will review the progress of the trial and safety of participants annually to discuss study progress, any safety concerns that have arisen, and make recommendations to improve safety procedures if indicated. The PIs will consult with the DSMB more frequently if safety issues arise or if it would be beneficial to obtain additional input from the DSMB.

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