

## ***REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (RTMS) FOR OBSESSIVE-COMPULSIVE DISORDER (OCD)***

**Regulatory Sponsor (S-I):** Sameer Sheth, MD, PhD  
**Co-Investigator:** Yagna Pathak, PhD  
**Study Product:** Brainsway™ cingulate coil (HAC coil)  
**Protocol Number:** AAAQ8771

## Study Summary

<b>Title</b>	Repetitive Transcranial Magnetic Stimulation (TMS) for Obsessive-Compulsive Disorder (OCD)
<b>Short Title</b>	rTMS for OCD
<b>Protocol Number</b>	Initial version
<b>Methodology</b>	Open-label study to investigate the feasibility and effectiveness of administering rTMS to patients suffering from OCD.
<b>Study Duration</b>	Study duration will be 3 weeks
<b>Study Center(s)</b>	Single-center
<b>Objectives</b>	The goal of the study is to assess whether repetitive transcranial magnetic stimulation (rTMS) can be used as a non-invasive option to benefit patients suffering from Obsessive Compulsive Disorder (OCD)
<b>Number of Subjects</b>	15
<b>Diagnosis and Main Inclusion Criteria</b>	Obsessive-compulsive disorder
<b>Study Product and Planned Use</b>	Brainsway™ HAC-coil to target the cingulate cortex
<b>Reference therapy</b>	N/A
<b>Statistical Methodology</b>	Statistics will be computed to observe changes within subjects and between subjects to assess the effectiveness of rTMS

## 1 Introduction

### 1.1 Background

With a prevalence of nearly 3%, obsessive-compulsive disorder (OCD) is one of the most common psychiatric disorders in the US (1). Its clinical manifestation includes persistent, intrusive and irrational thoughts, such as obsessions, and repetitive behaviors, i.e., compulsions, that cause distress and impairment for the individual (2). From an international perspective, the WHO has reported that OCD accounts for approximately 1% of global years lost due to disability (1). Thus, it is a disease with notable socioeconomic impact both on a national and global scale.

The first line of treatment for OCD comprises pharmacotherapy with serotonin reuptake inhibitors (SRIs) and cognitive behavioral therapy (CBT). Although adherence to these therapies has been shown to improve symptoms in at least half of patients, 30-40% have residual symptoms (3) and 10-15% are refractory to standard therapies (4). Options are limited, but do exist for treatment-refractory patients or individuals with residual symptoms. Although the mechanisms of action are not fully understood, deep brain stimulation (DBS) (5, 6) and stereotactic lesions (7, 8) represent two invasive interventions that have shown promise in alleviating residual or refractory OCD symptoms.

However, transcranial magnetic stimulation (TMS) may offer an alternate, less-invasive therapy. Repetitive TMS (rTMS) has been the most studied non-invasive modality in the OCD population, and preliminary data

demonstrate varying degrees of success (9). rTMS hyperpolarizes and depolarizes targeted brain regions by delivering magnetic current through a coil (10-11).

The symptoms of OCD are a result of generalized deficits in cognitive control, defined as the processes that enable pursuit of a goal while overcoming strong, automatic competing influences (12). Response inhibition is an executive cognitive process and one aspect of cognitive control that has been shown to be deficient in OCD patients (13-15).

The dorsal anterior cingulate cortex (dACC) and its associated neurocircuitry play an important role in cognitive control. Neuroimaging studies (fMRI and PET) have shown the dACC to be hypermetabolic in individuals suffering from OCD (16-25). The inputs to and projections from dACC suggest that it may be a cognitive control “hub,” such that it would integrate incoming signals and in effect weigh the costs and benefits of exerting control, termed expected value of cognitive control (12). There is evidence to support this putative role for dACC at the level of neuroanatomy, neurophysiology, and functional imaging (26-29). Deficient fear extinction may also be present in patients with OCD as demonstrated by studies showing decreased activation of dACC in fMRI during fear conditioning tasks (30). Finally, it has also been observed that OCD individuals are less quick to change behavior after making a mistake on a task, and such cognitive inflexibility is associated with altered fMRI activation of dACC and other cortical areas (31-32).

Electroencephalography (EEG) can be used to measure event-related potentials (ERPs) associated with cognitive control signals. Specifically, error-related negativity (ERN) signals that have been localized to dACC (33), are produced during tasks that involve cognitive control (34), and have been found to have increased amplitude in OCD patients, perhaps reflecting overactive error monitoring (35-37). Evidently, increase in the “frontal midline theta” power correlates with clinical measures of anxiety and conflict (34).

To summarize, rTMS can serve as a promising neuromodulatory intervention to manage refractory and residual symptoms associated with OCD. It can non-invasively target dACC, the putative “hub” for the cognitive processes, i.e., cognitive control, that are deficient in OCD patients. The present proposal is aimed at examining the effect of rTMS delivered with an H1 coil at the dACC on neurophysiological activity during a cognitive control task, as measured with fMRI and EEG.

## **1.2 Investigational Device**

The coil used in the study to apply rTMS is an H1-coil geometry manufactured by Brainsway™, specifically to target the cingulate cortex (HAC, Brainsway™ cingulate coil). The design of the coil is patented and aimed to induce stimulation at deeper regions without over-stimulating facial nerves or other superficial cortical regions. While not approved for OCD yet, the H-coil has received an IDE for cocaine addiction and was IDE exempt for marijuana addiction. The rTMS coil includes a flexible base shaped to fit the human head. The base is optimally fitted to the scalp at the desired region. This coil will be used in conjunction with a Magstim Rapid Stimulator (Magstim Company Limited, Whitland, UK).

## **1.3 Preclinical Data**

The abnormal neural circuitry that exists in OCD involves a relative decrease in glutamatergic signaling and grey matter within the dACC compared to healthy controls. rTMS has been explored as a method of treatment for cases of OCD that are refractory to medical treatment. Rupp et al used a rodent model to discern the pattern of brain activation after subjecting the animals to rTMS. The researchers used a round coil to deliver 25-Hz pulses for 2 seconds, then euthanized and decapitated the animals 45-60 minutes later to examine their brain tissue. They found that the rats subjected to rTMS had increased cfos expression in the cingulate, primary and secondary motor cortices, suggesting that these areas were selectively stimulated by rTMS. Expression was greatest in the ACC. This shows promise for targeting the dACC in OCD patients (38). Several OCD animal models have demonstrated that applying high frequency stimulation to certain areas of the brain, such as the subthalamic nucleus and the nucleus accumbens, can decrease compulsive behavior. Kupsch et al subjected quinpirole-induced rats to high frequency stimulation (130Hz) to functionally inhibit the subthalamic nucleus and observed significantly

decreased compulsive checking behavior (39). Winter et al later applied the same high frequency stimulation to the nucleus accumbens via deep brain stimulation and also observed significantly decreased compulsive checking (40). It can be inferred that applying similar electrical stimulation to modulate dACC circuitry may also yield significant reductions in the severity of OCD symptoms.

#### **1.4 Clinical Data to Date**

An initial feasibility study was conducted with the Brainsway™ H1-coil at the NIH on 6 healthy volunteers. The device was determined to be non-significant risk (NSR) and therefore, the trial was conducted under an IRB approval. Another safety study was conducted in 2005 at the Shalvata Mental Health Center, Hod Ha Sharon, Israel. The study compared H1-coil, H2-coil, standard figure-8 coil and a sham coil in healthy subjects. Additionally, Brainsway™ has also conducted a clinical study for the indication of MDD. This study is summarized in their IDE and a recent publication (41).

The aforementioned pilot and feasibility studies confirm the safety profile of the coil. It should be noted, that the parameters that will be employed in our OCD study, while different from those of the MDD study, comply with the safety guidelines recommended by the manufacturer.

#### **1.5 Research Risks & Benefits**

##### **1.5.1 Risk of Investigational Device**

The risks of rTMS include seizures, headaches, and hearing problems. Since the rTMS induces an electrical field on the brain, the most serious risk is the possibility of having a seizure.

The rTMS coil that is being used in this study is called the "HAC coil". While rTMS has been approved by the FDA for some neuropsychiatric indications such as MDD, this particular coil is experimental and has not yet been approved by the FDA for OCD. Seizures from any kind of rTMS treatment are rare and occur at a rate of about 2/1000. In people who received rTMS in the past with similar intensity and the same Hcoil we will be using in this study, three out of more than 200 people had a seizure. Patients experiencing adverse effects were on certain medications that made them more prone to seizures. In order to minimize the risk for seizures, patients will not be able to participate in this study if they have a medical or psychiatric condition that requires them to take certain medications regularly. Patients will also not be allowed to participate if they have a family history of seizures. A physician will be present during each rTMS treatment and will provide necessary care in case of adverse events. Additionally, suicidal ideation and emergence of manic symptoms following rTMS treatment are also potential risks. Should any of these occur, patients will not be able to continue with the remainder of the study.

There is also a risk of hearing problems (hearing loss or ringing in the ears) after rTMS. This problem is less likely to occur with the proper use of earplugs. The most common risk of rTMS is the possibility of having a headache after the sessions. Over the counter pain medicines (like ibuprofen or acetaminophen) can be taken if needed. Additional risks include scalp and dental pain, which can be treated with over the counter pain medications also. In case of any other adverse events, rTMS will be stopped and patient will be monitored closely.

##### **1.5.2 Other Risks of Study Participation**

While there have been no reports of any harmful long-term effects caused by the MRI scanner, including magnets of high strength, the long-term effects of being placed in a magnet of the strength used in this study are unknown. Although there are no known risks associated with pregnancy, females cannot participate in this study if pregnant. A negative pregnancy test (urine analysis) is required at the time of screening as well as the day of the fMRI scans.

Some people have reported sensations during MRI scans, such as "tingling" or "twitching" (or, very rarely, a painful sensation), which are caused by changes in the magnetic field that can stimulate nerves in your

body. With any MRI scan, on occasion, some people experience nervousness or discomfort due to the scanner's small space and the need to lie still. Except for pacemakers, some types of metallic implants, and medication patches, we are not aware of any other potentially dangerous interactions or hazards associated with the MRI scan. The MRI scanner also produces a loud noise; earplugs will be provided to reduce this discomfort. It may be uncomfortable to lie motionless in the scanner, and it may cause the patient to feel anxious. A member of the research staff will be available to provide support.

The only risk associated with psychological testing and behavioral assessment is potential nervousness/frustration with the tasks. The research team will thoroughly explain the tests and will be available to answer questions that may arise during tasks.

### 1.5.3 Potential benefits

Throughout the course of the study, rTMS may decrease symptoms associated with OCD. rTMS may also ease the patient's ability to engage in cognitive behavior therapy (CBT), which may also help control their symptoms. However there is a possibility of no therapeutic effect for OCD, and therefore there might be no direct benefit to the patient.

As a benefit to the OCD patient cohort, neuroimaging during this study will be used to evaluate rTMS as a screening procedure to help determine which patient populations might derive the most benefit from currently implemented invasive treatment options such as cingulotomy or DBS. Likewise, findings from neuroimaging and EEG will also add to our knowledge of the circuit involved in OCD by assessing acute and longitudinal biomarkers.

## 2 Study Objectives

The purpose of this study is to understand how rTMS might best benefit patients suffering from disorders of the dACC. In particular, we will determine how rTMS affects patients with OCD. We also aim to evaluate rTMS as a screening procedure to help determine which patient populations might derive the most benefit from currently implemented invasive treatment options such as cingulotomy or DBS. Lastly, we will study how neuromodulation affects the circuitry of the brain by assessing acute and longitudinal biomarkers from neuroimaging.

## 3 Study Design

### 3.1 General Design

rTMS delivery: High-frequency (10 Hz) deep TMS will be administered at the dACC to patients over 3 weeks using the HAC-coil (Brainsway™ cingulate coil) designed specifically to target the cingulate cortex and the Magstim Rapid stimulator (Magstim Company Limited, Whitland, UK). Sessions will be administered five times a week with a total of 15 visits. The intensity of stimulation will be relative to resting motor threshold (110%). Forty 3-second trains with an inter-train period of 20 seconds will be applied. Total number of pulses administered will be 1200. Periodic weekly behavioral assessments will be performed with the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) to monitor OCD symptoms. We will also test for suicidal ideation (C-SSRS) and monitor manic symptoms (YMRS) twice a week in addition to baseline and at the end of treatment course (x 8 total) and test cognitive function with Minimental status examination (MMSE). Subjects will be compensated for their daily visits in order to offset inconvenience related to time, effort and transportation costs. They will receive \$100 per fMRI session (x2 total) plus \$40 per TMS session (x15 total) over the study period.

Neuropsychological scales and tests: Neuropsychological evaluations will be administered at baseline and at the end of the study.

1. Scales (expected to take 30-40 minutes total):

- USP-Sensory Phenomena Scale

- Hamilton Depression Rating Scale
- Hamilton Anxiety Rating Scale
- Beck Anxiety Inventory
- Beck Depression Inventory, 2nd Edition
- Sheehan Disability Scale
- Barratt Impulsiveness Scale (BIS -11)
- Clinical Global Impression (CGI)
- Quality of Life Enjoyment and Satisfaction- short form (Q-LES)

2. Neuropsychological measures (expected to take about 90 minutes and can be performed in separate sessions as needed):

- Wechsler Abbreviated Scale of Intelligence (WASI)
- WMS-III Faces, LM, Digit Span, Spatial Span, LNS
- Rey Osterrieth Complex Figure (ROCF)
- California Verbal Learning Test, 2nd Edition (CVLT-II)
- Iowa Gambling Test (IGT)
- Wisconsin Card Sort Task (WCST)
- Judgment of Line Orientation
- Boston Naming Test
- DKEFS Verbal Fluency, Trails, Color Word Interference Test
- Grooved Pegs

Multi-Source Interference Task (MSIT): We will use the multi-source interference task (MSIT) to engage the dACC and study cognitive control in OCD. The MSIT combines elements of Simon and Ericksen flanker tasks. A 3-number cue is presented to the subject on a screen. Of the three numbers, 2 are the same and represent 'distractors'. The unique different number is the 'target'. The patient is instructed to press the button corresponding to the 'target' number (left button if the target is '1', middle if '2', right if '3'). Importantly, the subject should push the button corresponding to the target regardless of where that target is in the sequence. Four levels of conflict are presented:

- 1) No conflict: Distractors are absent and target is in correct spatial location (ex: 020)
  - 2) Flanker Interference: Distractors present and target is in correct spatial location (ex: 121)
  - 3) Spatial Interference: Distractors are absent, but target is not in correct spatial location (ex: 200)
  - 4) Both Interference: Distractors are present and target is not in correct spatial location (ex: 211)
- Behavior will be quantified based on response accuracy and reaction time during the task. These results will be correlated with changes in Y-BOCS and changes in neuroimaging to determine the effect of rTMS on cognitive control in OCD.

Simultaneous fMRI/EEG scans along with structural and diffusion MRI will be acquired at the beginning and end of treatment protocol. Pre and post-TMS EEG will also be collected 2 times a week.

Neuroimaging and Neurophysiology: High resolution (3T) structural MRI will be acquired along with DTI at the beginning and completion of treatment. Also, a simultaneous fMRI-EEG (40 channels) scan will be acquired at these times while the patient is completing the MSIT. An EEG-based fMRI analysis will help us overcome limitations of spatial and temporal resolution that are evident when using either technique alone. A data-driven approach will be used to identify temporally specific and task-relevant projections of the EEG data, which will then be used to construct fMRI regressors. This approach will allow us to link BOLD correlates with task engagement, which is not possible with traditional acquisitions. Further, it will enable us to study trial-to-trial variability as we can measure both the amplitude and variance of the ERPs.

Additionally, pre-rTMS and post-rTMS high-density scalp EEG data (128 channels) will be acquired two times a week for a total of 12 EEG acquisitions. The patient will be engaged in the MSIT during EEG acquisitions. EEG analysis will be used to quantify acute effects of rTMS by exploring within-session data,

and longitudinal effects of rTMS by exploring between-session data. The high-density acquisition will also allow for a thorough analysis in sensor and source domains.

Data Analysis: fMRI regressors will be constructed at multiple offsets in the epoched EEG data to view the temporal progression of the discriminating components (Walz 2013). Linear classifiers will be trained on EEG data to estimate a set of spatial weights to maximize discrimination of 2 conditions. Regressors will also account for single-trial variability. Lastly, we will compute ICA-based source localization on the fMRI data to extract the nodes of the underlying network evoked during this task.

For the EEG analysis, we will first analyze the data in sensor domain and assess the effect of rTMS by computing differences in ERPs and midline frontal theta. This initial analysis will then be used to reconstruct source signal. Region-specific measures (power) and connectivity measures (frequencydependent coherence) will also be computed. Although EEG measures correspond to a fraction of total synaptic action in a particular tissue volume, strong correlations have been reported between cognitive processing and event-related potentials that occur due to interactions with background synaptic action fields. Therefore, by extending our measures from source activity to source connectivity, we can indirectly measure changes in synaptic plasticity.

Each patient will serve as their own control and statistical comparisons will be made between measures at baseline and at the end of the TMS protocol (3 weeks). Although this study design doesn't address time-effects, we believe it is a crucial first step towards a better understanding of the effects of TMS.

*Effectiveness Variables:*

- 1) Changes in midline frontal theta and ERPs will be compared pre and post rTMS for OCD
- 2) Changes in dACC connectivity with frontal regions (DLPFC and OFC) will be assessed over the course of rTMS treatment for OCD
- 3) Changes in YBOCS will be assessed over the course of rTMS as a measure of secondary effectiveness. Clinical response will be defined as 35% reduction in YBOCS from baseline.

### **3.2 Primary Safety Endpoints**

According to the safety guidelines recommended by Brainsway™ corresponding to the HAC coil, 3 weeks is an acceptable study duration with the investigational HAC-coil. Brainsway™ has performed studies in control subjects and in subjects with clinical conditions (MDD, schizophrenia, bipolar disorder, addiction, PTSD) (Brainsway, Ltd. Unpublished data). They have currently tested 209 subjects (98 without concomitant psychotropic medication; 111 with psychotropic medication) with high-frequency, highintensity rTMS. Of the subjects who were still taking psychotropic medications that could lower seizure thresholds, 3 suffered a seizure. Should the patient experience adverse effects prior to completion of study, their participation will be discontinued in lieu of their safety. Additionally, we will account for the incidence, severity and frequency of all Adverse Events (AEs), including seizures and suicidality (i.e., suicide attempts and completed suicides).

## **4 Subject Selection and Withdrawal**

CRITERION	METHOD OF ASCERTAINMENT
<b><u>Inclusion:</u></b>	
1) Male or female outpatients, 18 to 65 years of age.	Self report
2) Primary diagnosis of Obsessive Compulsive Disorder, as confirmed by the Structured Clinical Interview for the DSM-V-TR (SCID).	SCID, DSM-IV-TR

3) Subjects should have at least a moderate level of OCD severity as defined by a Yale-Brown Obsessive Compulsive Disorder Scale (YBOCS) score of greater than 10 on either obsession section or compulsion section (YBOCS-O $\geq$ 10 or YBOCS-C $\geq$ 10).	YBOCS
3) Patients currently on OCD medication must be at the same stable dose(s) and be willing to continue the same dose(s) through the duration of the study.  Note: Subjects should be maintained on SSRI medications (with or without additional antidepressant or psychotropic augmentation for treatment of OCD) at a stable therapeutic dosage for at least 2 months prior to study entry and for the duration of the trial, and/or subjects are maintained on psychotherapeutic behavioral intervention therapy (subjects undergoing CBT treatment must be in the maintenance stage and not in the assessment or skills acquisition or training stages).	Physician Evaluation
4) Patients must continue to be under the care of their treating psychiatrist who will be writing prescriptions for concomitant medications through the duration of the study.	Physician Evaluation
5) Capable and willing to provide informed consent	Physician Evaluation
6) Signed HIPAA authorization	Physician Evaluation
<b><u>Exclusion:</u></b>	
1) Investigators, and their immediate families (defined as spouse, parent, child or sibling, whether by birth or legal adoption).	Self Report
2) Individuals diagnosed by the investigators with the following conditions: Bipolar Disorder (lifetime), any Psychotic Disorder (lifetime), history of substance abuse or dependence within the past year (except nicotine and caffeine).	Physician Evaluation, SCID, DSMIV-TR
3) An Axis II Personality Disorder, which in the judgment of the investigator may hinder the patient in completing the procedures required by the study protocol.	Physician Evaluation, Private Psychiatrist Reports
4) Individuals with a clinically defined neurological disorder including, but not limited to: stroke, tics, space occupying brain lesion, any history of seizures except those therapeutically induced by ECT, history of cerebrovascular accident, transient ischemic attack within two years, cerebral aneurysm, dementia, Parkinson's Disease, Huntington Chorea, Multiple Sclerosis.	Physician Evaluation, Medical Records
5) Increased risk of seizure for any reason, including prior diagnosis of increased intracranial pressure (such as after large infarctions or trauma), or history of significant head trauma with loss of consciousness for $\geq$ 5 minutes.	Patient Reports
6) History of treatment with rTMS therapy for any disorder.	Patient Reports



Subjects with positive responses to the Transcranial Magnetic Stimulation Adult safety screen (TASS, enclosed)	TASS
7) History of treatment with Deep Brain Stimulation.	Patient Reports
8) Use of any investigational drug within 12 weeks of the randomization visit.	Patient Reports
9) Current use of any medications with proconvulsive action, such as bupropion, maprotiline, tricyclic antidepressant, clomipramine, classical antipsychotics.	Physician Evaluation, Medical Records
10) Inability to obtain a motor threshold in patients due to chronic use of a medication (eg. anticonvulsants, benzodiazepines, sedative/hypnotics and atypical antipsychotics)	Physician Evaluation, Medical Records
11) Significant acute suicide risk, based on the current state or recent history using Columbia Suicide Severity Rating Scale (CSSRS).	C-SSRS
12) Cardiac pacemakers, implanted medication pumps, intracardiac lines, or acute, unstable cardiac disease.	Physician Evaluation
13) Intracranial implants (e.g. aneurysm clips, shunts, stimulators, cochlear implants, or electrodes) or any other metal object within or near the head, excluding the mouth, that cannot be safely removed.	Physician Evaluation
14) If participating in psychotherapy, must have been in stable treatment for at least three months prior to entry into the study, with no anticipation of change in frequency of therapeutic sessions, or the therapeutic focus over the duration of the rTMS trial.	Private Psychiatrist Reports
15) Current illicit drug use.	Physician Evaluation and urine drug screen
16) Current significant laboratory abnormality.  Note: Clinically significant laboratory abnormality refers to patient lab results that fall outside the established normal ranges, may be indicative of the presence of a medical condition, and are not thought to reflect an artifact or routine lab error (e.g. hemolysis). Results of laboratory tests are reviewed by the study physician prior to any treatment. Abnormal lab results of clinical significance that cannot be resolved (e.g. by repeating the test to rule out laboratory error or poor quality of the original sample) will lead to exclusion from the study.	Physician Evaluation
17) Known or suspected pregnancy.	Urine pregnancy test
18) Women who are breast-feeding.	Self Report
19) Women of childbearing potential not using a medically accepted form of contraception when engaging in sexual intercourse.	Self Report

### **Patient Discontinuation:**

A subject will be discontinued from the study for any of the following reasons:

- Inability to locate and quantify a motor threshold (MT) as defined in the protocol.
- The investigator decides that the patient should be withdrawn for the safety and welfare of the patient. For example, the patient experiences a clinically significant adverse event that is inconsistent with continuation in the study.
- The patient withdraws consent.
- Subject has significant tremor in any limb.
- Subject experiences a seizure.
- Subject has an elevated risk of suicide, based on results from the Columbia Suicide Severity Rating Scale (C-SSRS) and/or psychiatric interview or attempts suicide after receiving rTMS. The study investigator should refer the subject to his/her primary psychiatrist or inpatient hospitalization in case the patient is discontinued from the study.
- Subject becomes pregnant.

The safety of the patient following their discontinuation will be ensured by their primary physician.

## **5 Study Device**

### **5.1 Description**

The study device is a rTMS HAC-coil manufactured by Brainsway™ to target the dACC. This will be used with the Magstim Rapid Stimulator. The coil and the stimulator are the major components of the system. Stimulation paradigm can be programmed before the patient arrives to deliver trains at a specific frequency. See section 1.2 or the attached manual for details.

### **5.2 Treatment Regimen**

Patients will undergo 3 weeks (5x per week) of high-frequency (10-Hz) rTMS at the dACC interspersed with EEG and neuroimaging acquisitions. The protocol will be administered at the Psychiatric Institute. The intensity of stimulation will be based on resting-motor threshold (RMT). If the patient is unable to tolerate the intensity, this parameter may be reduced to make the patient more comfortable.

### **5.3 Prior and Concomitant Therapy**

- See section 4.

### **5.4 Receiving, Storage, Dispensing and Return**

#### **5.4.1 Receipt of Study Device**

The device is currently on the medical campus.

#### **5.4.2 Storage**

The stimulation set-up is currently housed at the New York State Psychiatric Institute on the third floor. Trained investigators or physicians will have access to the setup and will administer the stimulation. A physician will be present during rTMS sessions to ensure patient safety.

## **6 Study Procedures**

	Monday	Tuesday	Wednesday	Thursday	Friday
<b>Baseline</b>	Neuroimaging, Neurophysiology and Neuropsychiatry evaluations				
<b>Week 1</b>	rTMS	rTMS preTMS EEG postTMS EEG MMSE, YMRS, CGI, CSSRS	rTMS	rTMS preTMS EEG postTMS EEG YBOCS, MMSE, YMRS, CGI, CSSRS	rTMS
<b>Week 2</b>	rTMS	rTMS preTMS EEG postTMS EEG MMSE, YMRS, CGI, CSSRS	rTMS	rTMS preTMS EEG postTMS EEG YBOCS, MMSE, YMRS, CGI, CSSRS	rTMS
<b>Week 3</b>	rTMS	rTMS preTMS EEG postTMS EEG MMSE, YMRS, CGI, CSSRS	rTMS	rTMS preTMS EEG postTMS EEG YBOCS, MMSE, YMRS, CGI, CSSRS	rTMS
<b>Follow-up</b>	Neuroimaging, Neurophysiology and Neuropsychiatry evaluations				

## 7 Statistical Plan

Statistical analyses with time series data and factor analysis will be carried out both within subject (to assess reliability of the observed effects across trials) and across subjects (to assess the generalizability across participants). Sample sizes are chosen based on expected effect sizes and the large heterogeneity in this subject population.

## 8 Safety and Adverse Events

### 8.1 Definitions

**Unanticipated adverse device effect (UADE):** Any serious adverse effect on health or safety or any lifethreatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or IDE application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

**Associated with the investigational device:** There is a reasonable possibility that the adverse effect may have been caused by the investigational device.

**Life-threatening adverse effect:** Any adverse effect that places the subject, in the view of either the investigator or the sponsor, at immediate risk of death from the effect **as it occurred**. It does not include a reaction that, had it occurred in a more severe form, might have caused death.

**Serious adverse effect:** An adverse effect is considered “serious” if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- death
- a life-threatening AE

- inpatient hospitalization or prolongation of existing hospitalization • a persistent or significant disability/incapacity
- a congenital anomaly/birth defect.

**Unanticipated adverse effect:** Any adverse effect, the nature, specificity, severity, or frequency of which is not consistent with the risk information in the clinical study protocol or elsewhere in the current IDE application.

## **8.2 Recording of Adverse Device Effects**

All observed or volunteered adverse effects (serious or non-serious) and abnormal test findings, regardless of treatment group, if applicable, or suspected causal relationship to the investigational device or, if applicable, other study treatment or diagnostic product(s) will be recorded in the subjects' case histories. For all adverse effects, sufficient information will be pursued and/or obtained so as to permit 1) an adequate determination of the outcome of the effect (i.e., whether the effect should be classified as a serious adverse effect) and; 2) an assessment of the causal relationship between the adverse effect and the investigational device or, if applicable, the other study treatment or diagnostic product(s). Adverse effects or abnormal test findings felt to be associated with the investigational device or, if applicable, other study treatment or diagnostic product(s) will be followed until the effect (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the sponsor-investigator.

## **8.3 Reporting of Adverse Device Effects and Unanticipated Problems**

### **8.3.1 Investigator reporting: Notifying the IRB**

The investigator will report any adverse events to the IRB as outlined in the IRB's Unanticipated Problems (UP) Policy.

### **8.3.2 Sponsor reporting: Notifying the FDA**

#### **FDA Reporting Process**

For any observed or volunteered adverse event that is determined to be a UADE, the sponsor-investigator will submit an expedited safety report to the FDA's Center for Devices and Radiological Health. The expedited safety report will consist of:

- a completed Form FDA 3500A
- a cover letter analyzing the significance of the event

A copy of this safety report will be provided to all participating study investigators.

The completed Form FDA 3500A and cover letter will be submitted to the FDA as soon as possible and, no, later than 10 working days after the sponsor-investigator first receives notice of the adverse effect.

If, following receipt and investigation of follow-up information regarding an adverse effect that was previously determined not to be a UADE, the sponsor-investigator determines that the event does meet the requirements for expedited reporting, the sponsor-investigator will submit a completed Form FDA 3500A and cover letter as soon as possible, but no later than 10 working days, after the determination is made.

Subsequent to the initial submission of a completed FDA Form 3500A, the sponsor-investigator will submit additional information concerning the reported adverse effect as requested by the FDA. Medical Device Reports, whether for anticipated or unanticipated device-related effects, are to be submitted on FDA Form 3500A. The contact information for submitting MDR reports is noted below:

Food and Drug Administration  
Center for Devices and Radiological Health

Medical Device Reporting  
PO Box 3002  
Rockville, MD 20847-3003

## **8.4 Stopping Rules**

The patient will be allowed to stop participating in the study at any point. Additionally, any safety considerations will be taken into account and the study will be stopped in accordance with patient comfort. More immediately, rTMS administration will be stopped in the occurrence of any adverse event (See section 4). Regarding the study, we will stop the study if serious AEs are observed in more than 3 subjects.

## **8.5 Medical Monitoring**

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 9 Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of adverse device events.

# **9 Data Handling and Record Keeping**

## **9.1 Confidentiality**

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). All study data will be coded with a unique alphanumeric identifier. The coded data will be stored on an end user device protected by a strong password. The key will be stored in an encrypted spreadsheet on an end-user device belonging to the primary investigator. All paper documents, including outcome measurement tools, consent and HIPAA forms will be maintained in a locked file cabinet. We will collect the minimum amount of information necessary for the purposes this study. Only approved study personnel will have access to this data, and all of the information gathered will be used for this study unless data has clinical relevance to the patient's treatment, in which case it will be shared with the patient's clinical team.

## **9.2 Source Documents**

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

## **9.3 Records Retention**

The sponsor-investigator will maintain records in accordance with 21 CFR 812, Subpart G.

# **10 Study Monitoring, Auditing, and Inspecting**

## **10.1 Study Monitoring Plan**

This study will be monitored in accordance to the monitoring plan described in Section 4. The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has

adequate space to conduct the monitoring visit. In addition, a monitoring log along with case report forms (CRFs) will be kept with research records.

## **10.2 Auditing and Inspecting**

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

## **11 Ethical Considerations**

This study is to be conducted according to US and international standards of Good Clinical Practice, applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Attachment for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The subject or legally acceptable surrogate will sign the consent form along with the investigator-designated research professional obtaining the consent.

Patients will be recruited directly by the clinician, who will ask potential subjects if they would like to enroll in the study. Appropriate candidates will be asked to participate using standard informed consent processes. We will emphasize the fact that the decision to participate in the study in no way will affect medical care or other services provided at our institution, and that participation in this research is completely voluntary.

An approved study investigator will obtain informed consent prior to patient enrollment, using Columbia University Medical Center IRB approval consent forms, which will be signed to indicate the participant's consent. The consent will include a description of the study and the data that will be gathered. The patient will be allowed to consent to any, all, or none of the parts of the study. Under no circumstances will consent be sought on the day of procedure.

## **12 References**

- 1) Ruscio, A. M., Stein, D. J., Chiu, W. T. & Kessler, R. C. The epidemiology of obsessive compulsive disorder in the National Comorbidity Survey Replication. *Molecular Psychiatry* 15: 53-63, (2010).
- 2) Association AP: Diagnostic and statistical manual of mental disorders. 4th ed. Washington, D.C., (2000).
- 3) Simpson HB. Response versus remission in obsessive-compulsive disorder. *The journal of clinical psychiatry* 67:269-276, (2006).
- 4) Garnaat, S. L. et al. Who qualifies for deep brain stimulation for OCD? Data from a naturalistic clinical sample. *The Journal of neuropsychiatry and clinical neurosciences* 26: 81-86, (2014).

- 5) Mallet, L. et al. Subthalamic nucleus stimulation in severe obsessive-compulsive disorder. *The New England journal of medicine* 359: 2121-2134, (2008).
- 6) Greenberg, B. D. et al. Three-year outcomes in deep brain stimulation for highly resistant obsessive-compulsive disorder. *Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology* 31: 2384-2393, (2006).
- 7) Lopes, A. C. et al. Treatment of resistant obsessive-compulsive disorder with ventral capsular/ventral striatal gamma capsulotomy: a pilot prospective study. *The Journal of neuropsychiatry and clinical neurosciences* 21: 381-392, (2009).
- 8) Lopes, A. C. et al. Gamma ventral capsulotomy for obsessive-compulsive disorder: a randomized clinical trial. *JAMA psychiatry* 71: 1066-1076, (2014).
- 9) Bais, M., Figeo, M. & Denys, D. Neuromodulation in obsessive-compulsive disorder. *The Psychiatric clinics of North America* 37: 393-413, (2014).
- 10) Walsh, Vincent, and Alan Cowey. Transcranial magnetic stimulation and cognitive neuroscience. *Nature Reviews Neuroscience* 1.1 (2000): 73-80.
- 11) Hallett, Mark. Transcranial magnetic stimulation and the human brain. *Nature* 406.6792 (2000): 147150.
- 12) Shenhav A, Botvinick Matthew M, Cohen Jonathan D. The Expected Value of Control: An Integrative Theory of Anterior Cingulate Cortex Function. *Neuron* 79: 217-240, (2013).
- 13) Chamberlain SR, Fineberg NA, Blackwell AD, Robbins TW, Sahakian BJ. Motor inhibition and cognitive flexibility in obsessive-compulsive disorder and trichotillomania. *The American journal of psychiatry* 163:1282-1284, (2006).
- 14) Liu Y, Gehring WJ, Weissman DH, Taylor SF, Fitzgerald KD. Trial-by-Trial Adjustments of Cognitive Control Following Errors and Response Conflict are Altered in Pediatric Obsessive Compulsive Disorder. *Frontiers in psychiatry* 3:41, (2012).
- 15) Yücel M, Harrison BJ, Wood SJ, Fornito A, Wellard RM, Pujol J, Clarke K, Phillips ML, Kyrios M, Velakoulis D, Pantelis C. Functional and biochemical alterations of the medial frontal cortex in obsessive-compulsive disorder. *Archives of general psychiatry* 64:946-955, (2007).
- 16) Adler CM, McDonough-Ryan P, Sax KW, Holland SK, Arndt S, Strakowski SM: fMRI of neuronal activation with symptom provocation in unmedicated patients with obsessive compulsive disorder. *Journal of Psychiatric Research* 34:317-324, 2000
- 17) Breiter HC, Rauch SL: Functional MRI and the study of OCD: from symptom provocation to cognitivebehavioral probes of cortico-striatal systems and the amygdala. *Neuroimage* 4:S127-138, 1996
- 18) Cheng Y, Xu J, Nie B, Luo C, Yang T, Li H, et al: Abnormal Resting-State Activities and Functional Connectivities of the Anterior and the Posterior Cortexes in Medication-Naïve Patients with Obsessive-Compulsive Disorder. *PLoS ONE* 8:e67478, 2013
- 19) Gruner P, Vo A, Argyelan M, Ikuta T, Degnan AJ, John M, et al: Independent component analysis of resting state activity in pediatric obsessive-compulsive disorder. *Hum. Brain Mapp.*:n/a-n/a, 2014
- 20) Maltby N, Tolin DF, Worhunsky P, O'Keefe TM, Kiehl KA: Dysfunctional action monitoring hyperactivates frontal-striatal circuits in obsessive-compulsive disorder: an event-related fMRI study. *Neuroimage* 24:495-503, 2005
- 21) Vriend C, Wit SJD, Remijnse PL, Balkom AJLMv, Veltman DJ, Heuvel OAvd: Switch the itch\_ A naturalistic follow-up study on the neural correlates of cognitive flexibility in obsessive-compulsive disorder. *Psychiatry Research: Neuroimaging* 213:31-38, 2013
- 22) McGuire PK, Bench CJ, Frith CD, Marks IM, Frackowiak RS, Dolan RJ: Functional anatomy of obsessive-compulsive phenomena. *The British Journal of Psychiatry* 164:459-468, 1994
- 23) Perani D, Colombo C, Bressi S, Bonfanti A, Grassi F, Scarone S, Bellodi L, Smeraldi E, Fazio F. [18F]FDG PET study in obsessive-compulsive disorder. A clinical/metabolic correlation study after treatment. *The British Journal of Psychiatry* 166:244-250, (1995).
- 24) Rauch SL, Shin LM, Dougherty DD, Alpert NM, Fischman AJ, Jenike MA: Predictors of fluvoxamine response in contamination-related obsessive compulsive disorder: a PET symptom provocation study. *Neuropsychopharmacology* 27:782-791, 2002

- 25) Swedo SE, Schapiro MB, Grady CL, Cheslow DL, Leonard HL, Kumar A, et al: Cerebral glucose metabolism in childhood-onset obsessive-compulsive disorder. *Arch Gen Psychiatry* 46:518-523, 1989
- 26) Sheth SA, Mian MK, Patel SR, Asaad WF, Williams ZM, Dougherty DD, Bush G, Eskandar EN. Human dorsal anterior cingulate cortex neurons mediate ongoing behavioural adaptation. *Nature* 488:218-221., (2012).
- 27) Hampton AN, O'Doherty J P. Decoding the neural substrates of reward-related decision making with functional MRI. *Proceedings of the National Academy of Sciences of the United States of America* 104:1377-1382, (2007).
- 28) Chein JM, Schneider W. Neuroimaging studies of practice-related change: fMRI and meta-analytic evidence of a domain-general control network for learning. *Brain research Cognitive brain research* 25:607-623, (2005).
- 29) Jessup RK, Busemeyer JR, Brown JW. Error effects in anterior cingulate cortex reverse when error likelihood is high. *J Neurosci* 30:3467-3472, (2010).
- 30) Milad MR, Furtak SC, Greenberg JL, Keshaviah A, Im JJ, Falkenstein MJ, et al: Deficits in Conditioned Fear Extinction in Obsessive-Compulsive Disorder and Neurobiological Changes in the Fear Circuit. *JAMA Psychiatry* 70:608, 2013
- 31) Veale DM, Sahakian BJ, Owen AM, Marks IM. Specific cognitive deficits in tests sensitive to frontal lobe dysfunction in obsessive-compulsive disorder. *Psychol Med* 26:1261-1269, (1996).
- 32) Gu B-M, Park J-Y, Kang D-H, Lee SJ, Yoo SY, Jo HJ, et al: Neural correlates of cognitive inflexibility during task-switching in obsessive-compulsive disorder. *Brain* 131:155-164, 2007
- 33) Dehaene S, Posner MI, Tucker DM. Localization of a Neural System for Error Detection and Compensation. *Psychological Science* 5:303-305, (1994).
- 34) Cavanagh JF, Shackman AJ. Frontal midline theta reflects anxiety and cognitive control: Metaanalytic evidence. *JOURNAL OF PHYSIOLOGY PARIS* 1-13, (2014).
- 35) Gehring WJ, Himle J, Nisenson LG. Action-monitoring dysfunction in obsessive-compulsive disorder. *Psychological Science* 11:1-6, (2011).
- 36) Johannes S, Wieringa BM, Nager W, Rada D, Dengler R, Emrich HM, Münte TF, Dietrich DE. Discrepant target detection and action monitoring in obsessive-compulsive disorder. *Psychiatry research* 108:101-110, (2001).
- 37) Santesso DL, Segalowitz SJ, Schmidt LA. Error-related electrocortical responses are enhanced in children with obsessive-compulsive behaviors. *Developmental neuropsychology* 29:431-445, (2006).
- 38) Ji, R. R., Schlaepfer, T. E., Aizenman, C. D., Epstein, C. M., Qiu, D., Huang, J. C., & Rupp, F. (1998). Repetitive transcranial magnetic stimulation activates specific regions in rat brain. *Proceedings of the National Academy of Sciences*, 95(26), 15635-15640.
- 39) Winter, C., Mundt, A., Jalali, R., Joel, D., Harnack, D., Morgenstern, R., ... & Kupsch, A. (2008). High frequency stimulation and temporary inactivation of the subthalamic nucleus reduce quinpirole-induced compulsive checking behavior in rats. *Experimental neurology*, 210(1), 217-228.
- 40) Mundt, A., Klein, J., Joel, D., Heinz, A., Djodari-Irani, A., Harnack, D., ... & Winter, C. (2009). Highfrequency stimulation of the nucleus accumbens core and shell reduces quinpirole-induced compulsive checking in rats. *European Journal of Neuroscience*, 29(12), 2401-2412.
- 41) Levkovitz, Y., Isserles, M., Padberg, F., Lisanby, S. H., Bystritsky, A., Xia, G., ... & Zangen, A. (2015). Efficacy and safety of deep transcranial magnetic stimulation for major depression: a prospective multicenter randomized controlled trial. *World Psychiatry*, 14(1), 64-73.