Neuroimaging in Patients Undergoing TMS for Depression

NCT02974296

Document Date: June 17, 2019

NEW YORK STATE PSYCHIATRIC INSTITUTE

INSTITUTIONAL REVIEW BOARD

MEMORANDUM

June 17, 2019

TO: Dr. Marta Moreno-Ortega

FROM: Dr. Edward V. Nunes, Co-Chair, IRB
Dr. Agnes Whitaker, Co-Chair, IRB

SUBJECT: **APPROVAL NOTICE: CONTINUATION*****

Your protocol # **7159** entitled **Neuroimaging in Patients Undergoing TMS for Depression** (version date 06-17-19) and consent forms have been approved by the New York State Psychiatric Institute - Columbia University Department of Psychiatry Institutional Review Board from **June 17, 2019 to May 25, 2020.** (Reviewed by the Full Board on 06-03-19.)

Consent requirements:

☐ Not applicable:

√ Signature by the person(s) obtaining consent is required to document the consent process.

☐ Documentation of an independent assessment of the participant's capacity to consent is also required.

Approved for recruitment of subjects who lack capacity to consent: √ **No** ☐ **Yes**

Field Monitoring Requirements: √ Routine ☐ Special:

√ **Only copies of consent documents that are currently approved and stamped by the IRB may be used to obtain consent for participation in this study.**

√ **A progress report and application for continuing review is required 2 months prior to the expiration date of IRB approval.**

√ **Changes to this research may be not be initiated without the review and approval of the IRB except when necessary to eliminate immediate hazards to participants.**

√ **All serious and/or unanticipated problems involving risks to subjects or others must be reported immediately to the IRB. Please refer to the PI-IRB website at http://irb.nyspi.org for Adverse Event Reporting Procedures and additional reporting requirements.**

*** *This protocol continuation has been approved with the modifications submitted on 05-23-19.*

CC: RFMH Business Office (NYSPI MRI center pilot hours; Internal funding (PI: Daniel Javitt))
CU Grants & Contracts (Neuronetics Inc.)

ENC: CF (version date 06-07-19 in compliance with revised Common Rule)
HIPAA Form
MRI letters

EN/AHW/Scr

Protocol Title:
Neuroimaging in Patients Undergoing TMS for Depression

Version Date:
06/17/2019

Protocol Number:
7159

First Approval:
05/26/2016

Expiration Date:
05/25/2020

Contact Principal Investigator:
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Co-Investigator(s):
Alayar Kangarlu, PHD
Jack Grinband, PHD
Daniel Javitt, MD, PHD

Research Chief:
Daniel Javitt, MD, PHD

Faculty Sponsor:
Daniel Javitt, MD, PHD

Cover Sheet

Choose ONE option from the following that is applicable to your study
If you are creating a new protocol, select "I am submitting a new protocol." As 5 Year Renewals are no longer required, this option remains for historical purposes.
I am submitting an annual continuation with modifications

Division & Personnel

Division

What Division/Department does the PI belong to?
Experimental Therapeutics
Within the division/department, what Center or group are you affiliated with, if any?
None

Unaffiliated Personnel

List investigators, if any, who will be participating in this protocol but are not affiliated with New York State Psychiatric Institute or Columbia University. Provide: Full Name, Degrees and Affiliation.

DR. Tarique Perera, MD, PhD.
Director, Contemporary Care Clinics

Amendment

Describe the change(s) being made
At NYSPI patients will only come for MRI. No patients will be treated at the NYSPI.
Provide the rationale for the change(s)
Patients will be treated off site by their referral psychiatrist.
Comment on the extent to which the proposed change(s) alter or affect risks/benefits to subjects
No risks/no benefits.
Comment on if the proposed change(s) require a modification to the Consent Form (CF)
No changes are needed. The MRI Scanning Consent Form will be used for both groups.

Application for Continuation of Research

Status

Current Status of Study:
Subject enrollment is ongoing.

Summary of Experiences to Date

Please provide a summary of scientific progress of the study and the experience of research participants, to date. This requirement is designed to allow for the investigator and the IRB to reassess the study's risks and benefits in terms of developments in the field, changing practice patterns, and new IRB policies and procedures.
We are in the recruitment phase. Patients' experience have been very pleasant and satisfactory.

Funding

Have there been any changes in funding status since the prior approval?
No
Have the principal investigator and other investigators made all required disclosures of financial interest in the study sponsor/product?
Yes

Summary

Have there been any study findings, recent literature, or untoward events occuring here or at other sites in the past year which might affect the analysis of the safety, risks or benefits of study participation?
No
Have there been any serious adverse events (serious and/or unanticipated problems involving risks to subjects or others at this site which occured in the past year)?
No
Have all study staff with a significant role in the design or implementation of the human subject components of this study received required training in human research subject protections?
Yes
Is the study covered by a certificate of confidentiality?
No

Overall Progress

Approved sample size
60
Total number of participants enrolled to date
28
Number of participants who have completed the study to date
26
Have there been any significant deviations from the anticipated study recruitment, retention or completion estimates?
Yes
Describe actions taken or planned to address these problems.

The upgrade of the scanner at NYSPI MRI required transferring our imaging protocol to CBIC MRI. The development of same protocol took extra time. The protocol is now developed and available.

The population of patients from Dr. Tarique Perera in Greenwich (Connecticut) who satisfy inclusion/exclussion criteria decreased. Other psychiatrists from his team will help with patients referral.

Comments / additional information

Sample Demographics

Specify population
Depressed Adults prescribed for the first time to standard TMS
Total number of participants enrolled from this population to date
24
Specify population #2
Depressed Adults non-responders to standard TMS
Total number of participants enrolled from this population to date
10

Gender, Racial and Ethnic Breakdown

14 male, 14 women
26 caucasian, 2 other ethnic group

Summary of Current Year's Enrollment and Drop-out

Number of participants who signed consent in the past year
1
Number of participants currently enrolled
1
Did the investigator withdraw participants from the study?
No
Did participants decide to discontinue study involvement?
No

Procedures

To create the protocol summary form, first indicate if this research will include any of the following procedures

✓ MRI
✓ Off-label Use of Drug or Device

Population

Indicate which of the following populations will be included in this research

✓ Adults
✓ Adults over 50

Research Support/Funding

Will an existing internal account be used to support the project?
Yes
Describe internal account
1. NYSPI MRI center pilot hours.
2. Internal funding, Division of Experimental Therapeutics (retained clinical revenues, PI: Daniel Javitt)
Is the project externally funded or is external funding planned?
Yes

Select the number of external sources of funding that will be applicable to this study

Funding Source #1

Is the PI of the grant/contract the same as the PI of the IRB protocol?
Yes
Select one of the following
The grant/contract is currently funded
Source of Funding
Industry
Sponsor
Neuronetics Inc.
Is the study investigator initiated?
Yes
Select one of the following
Single Site
Business Office
CU
Does the grant/contract involve a subcontract?
No

Study Location

Indicate if the research is/will be conducted at any of the following
✓ NYSPI
This protocol describes research conducted by the PI at other facilities/locations
No

Lay Summary of Proposed Research

Lay Summary of Proposed Research
Repetitive transcranial magnetic stimulation (rTMS) is a novel method for treating depression, in which a magnetic coil is used to stimulate specific regions of the brain. Although the approach has proven effective for some individuals with medication-resistant depression others do not benefit from the TMS approaches that are presently being used. One reason why some people respond well and others do not may have to do with individual variations in brain organization, which would require stimulation to be applied to slightly different locations in different individuals. The differences in brain organization can be detected using individualized functional MRI scans, which then allow the coil placement to be determined separately for each individual. The goal of this project is to guide rTMS using fMRI in individuals with depression who did not respond to standard TMS treatment to evaluate whether targeted TMS using individualized functional MRI scans produce outcome superior to that of conventional approaches. We will also scan MDD patients prescribed to receive standard TMS for the first time before and after which they will have resting-

state FMRI scan in order to see if we can predict their responsiveness based on the functional connectivity maps.

This protocol will recruit subjects from an ongoing study of rTMS treatment of depression being conducted by Dr. Tarique Perera who is a non-Columbia physician, and already approved by an independent IRB (WIRB protocol #20141643 entitled: "Cognitive Changes During Treatment with TMS for Major Depression", see attachment).
Group 1 are patients coming from Dr. Perera's offices who will be scanned at the NYSPI MRI Unit pre/post TMS treatments. TMS treatments for this group will be implemented under Dr. Perera's protocol and WIRB. We will only be doing scanning at the NYSPI.
Group 2 are patients coming from Dr. Perera's offices who will come to the NYSPI site to be scanned at the NYSPI MRI Unit pre/post TMS treatments and to receive a second course of TMS. For Group 2, we will be doing both scanning and treatment.

Background, Significance and Rationale

Background, Significance and Rationale

Significance: There are few therapeutic options for individuals with treatment resistant depression (TRD). One recently developed approach is rTMS over left dorsolateral prefrontal cortex. Recent studies have demonstrated overall antidepressant benefit of rTMS in patients who fail to respond to a trial of antidepressant medication (1, 2, 3). Nevertheless, for many patients the response is incomplete, suggesting the need for further optimization. One potential cause of heterogeneous response might relate to individual differences in brain anatomy and connectivity patterns. At present, the rTMS stimulation site across subjects is based upon fixed location relative to motor cortex. Potentially, however, the approach could be optimized by stimulating based upon individual brain functional connectivity pattern. The present project will collect pre- and post-treatment brain functional connectivity measures in a group of patients who will be receiving independent clinical rTMS for resistant depression, a connectivity-based targeting approach will be applied at the single-subject level to individualize therapy in those patients who do not respond to standard approaches.

The present study is based upon the hypothesis that the clinical efficacy of rTMS reflects functional connectivity between left DLPFC and remote regions such as the subgenual cingulate (sgACC), and that the precise regions of DLPFC that are functionally connected to sgACC may differ across individuals (4, 5). Thus, individualized functional connectivity patterns using standard resting-state functional connectivity measures may assist in optimizing rTMS efficacy across individuals.

Background: The present research is based upon the theoretical conceptualization of depression as a network disorder that reflects alterations in function in a distributed network of regions including DLPFC (especially left), medial prefrontal and orbitofrontal cortices, sgACC, insula, thalamus, hypothalamus, and hippocampus (HPC). Retrograde tracer studies in nonhuman primates indicate that the DLPFC has reciprocal connections with sgACC (6, 7, 8, 9, 10). The sgACC is a key region within the frontolimbic network and has consistently been shown to be metabolically hyperactive during depressive episodes (11, 12-16, 14, 15, 17, 18). Voxel-by-voxel analyses of neurophysiological data from depressed samples versus controls localized the peak difference in activity to the sgACC (19). In general, effective antidepressant treatments attenuate this sgACC metabolic hyperactivity (20, 14, 16, 21), supporting the importance of this region. Nevertheless, because of its deep location sgACC cannot be directly targeted by non-invasive approaches such as TMS, and thus must be manipulated indirectly via networks that may themselves be dysfunctional in depression.

The present study is also motivated by extensive literature suggesting that effects of rTMS are not confined to the local area of stimulation, but instead propagate beyond the site of stimulation, impacting a distributed network of brain regions (22-25). These observations suggest that rTMS may relieve depression by modulating synaptic strength both locally and at distant sites modulating functional connectivity in cortical networks. Part of the antidepressant mechanism of DLPFC rTMS may be remote suppression of activity in the sgACC and other limbic regions (20, 26, 27). Fox et al. (23), showed that target sites with the best rTMS

antidepressant efficacy exhibited the strongest anticorrelated resting-state functional connectivity (rsFC) in the sgACC.
The present study will test this hypothesis on a group of patients with MDD non-responders to standard TMS by conducting pre-treatment functional connectivity to enable targeting of rTMS based upon individualized connectivity maps. These locations will then be used at the NYSPI site and also given to the treating physician (Tarique Perera) to optimize target for focal brain stimulation and efficacy across individuals. Of note, patients from group 1 will be scanned at the NYSPI site but will not receive treatment here, whereas group 2 will both be scanned and receive treatment.

Our preliminary data in Fig. 1 shows results acquired from a subset of patients with MDD that reveals an increase in anti-correlation between left-DLPFC and sgACC consecutive to convulsive therapy. These results suggest that ability to deliver TMS pulse to special targets identified on functional connectivity maps (e.g. DLPFC) have the potential to positively confirm their involvement in MDD. Increase in anticorrelation of rsFC signal of these regions after TMS would amount to such evidence. This is exactly what we observed in convulsive therapy as is shown in Fig 1 in which green-blue-purple spectrum on the sgACC rsFC maps are the surface vertexes within BA46 with highest anticorrelation BOLD signal with sgACC. We seek to replicate this effect with targeted TMS in non-responders to standard TMS. Such strategy has the potential to optimize therapeutic efficacy of TMS (see Fig. 1, attached).

Our justification for committing the non-responders to a second cycle of TMS is as following:
1) The second cycle will use an entirely different type of TMS, i.e. neuronavigated TMS based on the functional connectivity maps obtained from patients' brain which offers, hereto-forth, the best guide for the efficacy of TMS as shown in Fig. 1.
2) Since the patients for the second cycle are randomized to receive either neuronavigated or standard TMS, we can justify a second cycle of standard TMS by statistics from Dr Perera's clinics which are in agreement with application guidelines for the use of TMS (Rossi et al., 2009). As for Dr Perera's past experience is concerned, of the 139 patients that received 9 weeks of TMS, 60 responded at the 4 week point and 89 responded at the 8 week point. Of the 79 that did not respond at the 4 week measurement, 42 (more than 50%) responded at the week 8 point. Response is defined here as a 50% or greater reduction in starting Ham D score. As such, while the advantage of the second round of TMS is clear for the patients who receive neuronavigated TMS, even for the patients who receive the second round of standard TMS the above facts demonstrate the advantages of prolonged (4-8 week) treatment by TMS in the form of a 50% favorable outcome in that group of patients.

In addition to resting state functional connectivity, we will also assess glutamate (Glu) concentrations and resting-state cerebral blood flow/volume (rsCBF/rsCBV) in DLPFC and cortical midline structures (CMS) using Magnetic Resonance Spectroscopy (MRS) and Arterial Spin Labelling (ASL), respectively. CMS refer to brain structures situated near the medial wall of the brain and is mainly comprised of the ventral medial prefrontal cortex, dorsal medial prefrontal cortex, anterior cingulate cortex (the supragenual part in particular) and posterior cingulate cortex. Regional increases in Glu release increase the metabolic rate of post-synaptic neurons (28), and surrounding astrocytes (29), leading to regional BOLD signal increases (30). Glu concentrations may therefore be linked to overall functional connectivity patterns (31-34). In particular, Glu levels in left DLPFC in MDD provide an index of local metabolic activity, and abnormalities can be reversed in a dose-dependent manner by rTMS (35). These effects are present not only close to the stimulation site (left DLPFC), but also in remote (right DLPFC, left cingulate cortex) brain regions.

Abnormal reduction of sgACC cerebral blood flow (CBF) and glucose metabolism in MDD have also been found (36-39). These apparently discrepant results have been explained by the interrelationships between deficits in gray matter volume and physiological imaging data. The reduction in sgACC volume produce partial volume effects in functional brain images due to their relatively low spatial resolution, when this volumetric deficit is taken into account by correcting the metabolic data for the partial volume averaging effect associated with the corresponding gray matter reduction, metabolism instead appeared increased in the sgACC in the unmedicated-depressed phase and normal in the medicated-remitted phase (40).

Although MRS Glu levels and rsCBF/rsCBV will not be used to guide treatment location in the present study, nevertheless they will be analyzed to see if they can differentiate responders from non-responders to rTMS treatment approaches. fMRI, MRS and CBF/CBV procedures will be repeated following completion of the clinical protocol in order to evaluate potential clinical correlates of symptomatic improvement.

Specific Aims and Hypotheses

Specific Aims and Hypotheses
Specific aims of the project are as follows:

1) To conduct functional connectivity fMRI scans in a group of non-responders to standard TMS participating in an external rTMS clinical treatment protocol in order to permit individualized target location for targeted rTMS treatment. To personalize therapy, a functional connectivity-based targeting approach will be used to identify optimal TMS target coordinates in the left-DLPFC.

2) To determine whether fMRI functional connectivity, glu MRS and CBF/CBV abnormalities are associated with treatment outcome to rTMS.

3) To identify biological marker outcomes to treatment response as measured by 3-tesla MRI.

We hypothesize that individual differences in connectivity between DLPFC and sgACC are large and can be used to generate individualized TMS targets that will result in response rates higher than those traditionally associated with rTMS. In addition, we hypothesize that pretreatment DLFPC and CMS glu levels and CBF/CBV abnormalities will assist in identification of treatment-responsive subjects.

Description of Subject Population

Sample #1

Specify subject population
Depressed Adults prescribed for the first time to standard TMS
Number of completers required to accomplish study aims
60
Projected number of subjects who will be enrolled to obtain required number of completers
70
Age range of subject population
18-60

Sample #2

Specify subject population
Depressed Adults non-responders to standard TMS
Number of completers required to accomplish study aims
30
Projected number of subjects who will be enrolled to obtain required number of completers
35
Age range of subject population
18-60

Gender, Racial and Ethnic Breakdown

Given the gender difference in the prevalence of major depression, it is expected that approximately 2/3 of the sample will be female. Expected ethnic breakdown is: 80% Caucasian, 10% African-American, 10% Hispanic or other ethnic group.

Description of subject population
All patients will be adults aged 18-60 who are to receive targeted rTMS for their depressive symptoms. After passing all screening criteria, participants may still have their participation in the study ended if they do not comply with study procedures, if there is a change in their medical status, or if an adverse event has occurred.

Recruitment Procedures

Describe settings where recruitment will occur
Patients will be referred from private psychiatric facilities run by Tarique Perera, MD, and will be selected from those already participating in an approved clinical study of rTMS for treatment resistant depression (WIRB protocol #20141643 entitled: "Cognitive Changes During Treatment with TMS for Major Depression", see attachment).

How and by whom will subjects be approached and/or recruited?
Dr. Tarique Perera will tell potential participants about the current study, using the consent form cover sheet and flyers for patients and doctors to describe the types of procedures involved. Potential participants interested in learning more will receive Dr. Moreno's contact information from Dr. Perera to call and make an appointment at NYSPI for a visit with her and Drs. Stewart and Hellerstein. (Please find the Screening Phone call Script attached). Screening protocol from Jonathan W. Stewart's IRB # 6669R titled "Evaluation of Potential Participants for Depression Evaluation Service (DES) Research" will also be used.

How will the study be advertised/publicized?
The consent form cover sheet will be attached to other administrative forms that are part of the patients' office visits. An explanation illustrated with images will be presented to patients/controls by the PI previous to enrollment (attached). Flyers for patients and doctors are attached of review.
Do you have ads/recruitment material requiring review at this time?
No
Does this study involve a clinical trial?
Yes
Please provide the NCT Registration Number
NCT02974296

Concurrent Research Studies

Will subjects in this study participate in or be recruited from other studies?
Yes
Describe concurrent research involvement

WIRB Protocol #20141643, "Cognitive Changes During Treatment with TMS for Major Depression", Tarique Perera, MD, Principal Investigator; or

NYSPI IRB Protocol #6669R, "Evaluation of Potential Participants for Depression Evaluation Service (DES) Research", Jonathan Stewart, MD, Principal Investigator

If participants were enrolled in either of these studies and the screening evaluations were conducted within the prior six months, copies of all screening instruments will be made and reviewed by the study Principal Investigator. Eligibility would be determined based upon the results of the existing evaluations and the Principal Investigator will document their continued validity.

Inclusion/Exclusion Criteria

Name the subject group/sub sample
Depressed patients prescribed for the first time to standard TMS
Create or insert table to describe the inclusion criteria and methods to ascertain them

Eligibility screening may be conducted under
WIRB Protocol #20141643, "Cognitive Changes During Treatment with TMS for Major Depression", Tarique Perera, MD, Principal Investigator; or
NYSPI IRB Protocol #6669R, "Evaluation of Potential Participants for Depression Evaluation Service (DES) Research", Jonathan Stewart, MD, Principal Investigator
If participants were enrolled in either of these studies and the screening evaluations were conducted within the prior six months, copies of all screening instruments will be made and reviewed by the study Principal Investigator. Eligibility would be determined based upon the results of the existing evaluations and the Principal Investigator will document their continued validity.

Inclusion criteria
1. Male or female outpatients, 18 to 60 years of age. Self report
2. Primary diagnosis of Major Depressive Disorder as confirmed by the Structured Clinical Interview for DSM-IV Disorders (SCID-IV). SCID, DSM-IV
3. Duration of the index episode of at least 2 weeks. Psychiatric History
4. MDD symptoms, defined as a total HDRS-17 score ≥ 18 despite treatment with an adequate trial of a serotonin reuptake inhibitor (SRI). An adequte SRI trial is defined as treatment for at least 6-8 weeks on the SRI, that meets the maximum recommended dosage level for MDD (fluoxetine 40-60 mg/d, sertraline 100-200 mg/d, paroxetine 40-60 mg/d, fluvoxamine 200-300 mg/d, citalopram 40-60 mg/d, escitalopram 20-30 mg/d). We do not typically rely on an arbitrary upper cut-off on the HRSD because an arbitrary cut-off number would not capture the clinical salience of individual symptoms and clinical judgment must supersede (e.g. a HRSD of 18 but in the presence of active suicidal ideation and plan would exclude patient). HDRS-17/Clinician Psychiatric History
5. Individuals who cannot tolerate medications of class and dose at the specified duration defined in inclusion item #4. Psychiatric History
6. Patients currently on medication must be at the same stable dose(s) for 1 month prior to enrollment and be willing to continue at the same dose(s) through the duration of the study. Physician Evaluation
7. Capable and willing to provide informed consent Physician Evaluation
8. Signed HIPAA authorization. Physician Evaluation

9. Willingness to undergo research fMRI scan (3T).
10. Willingness to undergo randomization to either treatment arm.
11. Left/Right-handed. Edinburgh Handedness Questionnaire

Create or insert table to describe the exclusion criteria and methods to ascertain them

1. Investigators, and their immediate families (defined as a 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, DSM-IV
3. Behavior, 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: tics, space occupying brain lesion; any history of seizures except those therapeutically induced by ECT; history of cerebrovascular accident; history of fainting; transient ischemic attack within two years; cerebral aneurysm, Dementia; Parkinson's Disease; Hungtington 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 ≥ 5 minutes. Patients Reports
6. Use of any investigational drug within 12 weeks of the randomization visit. Patients Reports
7. Significant acute suicide risk, defined as follow: suicide attempt within the previous 6 months that required medical treatment; or ≥ 2 suicide attempts in the past 12 months; or in the investigator's opinion, has significant risk for suicide based on the current state or recent history. Physician Evaluation
8. Cardiac pacemakers, implanted medication pumps, intracardiac lines, or acute, unstable cardiac disease. Physician Evaluation
9. Intracranial implants (e.g. aneurysms 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 MRI Screening Form
10. Current illicit drug use (cannabinoid, phencyclidine, amphetamines, barbiturates, cocaine, methadone, and opiates), defined as drug use during the 6 months before screening. Physician Evaluation
11. Known or suspected pregnancy. Urine pregnancy test Women who are breast-feeding. Self Report
12. Women of childbearing potential not using a medically accepted form of contraception when engaging in sexual intercourse. Self Report
13. Medicinal patch, unless removed prior to the MR scan. Clinical interview
14. MDD patients with very severe depression, defined as a total HDRS-17 score ≥ 23, will be excluded and referred to immediate treatment.
15. Risks related to seizures, such as substance abuse or sleep disruptions/insomnia. Clinician Psychiatric History. SCID.
16. History of treatment with rTMS therapy for any disorder. Patients Reports.

Inclusion/Exclusion Criteria #2

Name the subject group/sub sample
Depressed patients non-responders to standard TMS
Create or insert table to describe the inclusion criteria and methods to ascertain them

Eligibility screening may be conducted under
WIRB Protocol #20141643, "Cognitive Changes During Treatment with TMS for Major Depression", Tarique Perera, MD, Principal Investigator; or
NYSPI IRB Protocol #6669R, "Evaluation of Potential Participants for Depression Evaluation Service (DES) Research", Jonathan Stewart, MD, Principal Investigator
If participants were enrolled in either of these studies and the screening evaluations were conducted within the prior six months, copies of all screening instruments will be made and reviewed by the study Principal Investigator. Eligibility would be determined based upon the results of the existing evaluations and the Principal Investigator will document their continued validity.

Inclusion criteria:
1. Male or female outpatients, 18 to 60 years of age. Self report
2. Primary diagnosis of Major Depressive Disorder as confirmed by the Structured Clinical Interview for DSM-IV-TR Disorders (SCID-IV-TR). SCID, DSM-IV-TR
3. Duration of the index episode of at least 2 weeks. Psychiatric History
4. MDD symptoms, defined as a total HDRS-17 score ≥ 18 despite treatment with an adequate trial of a serotonin reuptake inhibitor (SRI). An adequte SRI trial is defined as treatment for at least 6-8 weeks on the SRI, that meets the maximum recommended dosage level for MDD (fluoxetine 40-60 mg/d, sertraline 100- 200 mg/d, paroxetine 40-60 mg/d, fluvoxamine 200-300 mg/d, citalopram 40-60 mg/d, escitalopram 20-30 mg/d). We do not typically rely on an arbitrary upper cut-off on the HRSD because an arbitrary cut-off number would not capture the clinical salience of individual symptoms and clinical judgment must supersede (e.g. a HRSD of 18 but in the presence of active suicidal ideation and plan would exclude patient). HDRS-17/Clinician Psychiatric History
5. Individuals who cannot tolerate medications of class and dose at the specified duration defined in inclusion item #4. Psychiatric History
6. Patients currently on medication must be at the same stable dose(s) for 1 month prior to enrollment and be willing to continue at the same dose(s) through the duration of the study. Physician Evaluation
7. Capable and willing to provide informed consent. Physician Evaluation
8. Signed HIPAA authorization. Physician Evaluation
9. **Left/Right-handed. Edinburgh Handedness Questionnaire**
10. Willingness to undergo research fMRI scan (3T).
11. Willingness to undergo randomization to either treatment arm.
12. History of NON-response to rTMS in THIS depressive episode. Assessment of history from patient and/or Clinical Psychiatric History from Dr. Perara's office

Create or insert table to describe the exclusion criteria and methods to ascertain them

1. Investigators, and their immediate families (defined as a 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, DSM-IV-TR
3. Behavior, 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: tics, space occupying brain lesion; any history of seizures except those therapeutically induced by ECT; history of cerebrovascular accident; history of fainting; transient ischemic attack within two years; cerebral aneurysm, Dementia; Parkinson's Disease; Hungtington 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 ≥ 5 minutes. Patients Reports
6. Use of any investigational drug within 12 weeks of the randomization visit. Patients Reports
7. Significant acute suicide risk, defined as follow: suicide attempt within the previous 6 months that required medical treatment; or ≥ 2 suicide attempts in the past 12 months; or in the investigator's opinion, has significant risk for suicide based on the current state or recent history. Physician Evaluation
8. Cardiac pacemakers, implanted medication pumps, intracardiac lines, or acute, unstable cardiac disease. Physician Evaluation
9. Intracranial implants (e.g. aneurysms 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 MRI Screening Form
10. Current illicit drug use (cannabinoid, phencyclidine, amphetamines, barbiturates, cocaine, methadone, and opiates), defined as drug use during the 6 months before screening. Physician Evaluation
11. Known or suspected pregnancy. Urine pregnancy test Women who are breast-feeding. Self Report
12. Women of childbearing potential not using a medically accepted form of contraception when engaging in sexual intercourse. Self Report
13. Medicinal patch, unless removed prior to the MR scan. Clinical interview
14. MDD patients with very severe depression, defined as a total HDRS-17 score ≥ 23, will be excluded and referred to immediate treatment.
15. Risks related to seizures, such as substance abuse or sleep disruptions/insomnia. Clinician Psychiatric History. SCID.

Waiver of Consent/Authorization

Indicate if you are requesting any of the following consent waivers
Waiver of consent for use of records that include protected health information (a HIPAA waiver of Authorization)
No

Waiver or alteration of consent
Yes
Waiver of documentation of consent
No
Waiver of parental consent
No

Consent Procedures

Is eligibility screening for this study conducted under a different IRB protocol?
Yes
Indicate NYSPI IRB #
6669R
Describe Study Consent Procedures

Eligibility screening may be conducted under
WIRB Protocol #20141643, "Cognitive Changes During Treatment with TMS for Major Depression", Tarique Perera, MD, Principal Investigator; or
NYSPI IRB Protocol #6669R, "Evaluation of Potential Participants for Depression Evaluation Service (DES) Research", Jonathan Stewart, MD, Principal Investigator
If participants were enrolled in either of these studies and the screening evaluations were conducted within the prior six months, copies of all screening instruments will be made and reviewed by the study Principal Investigator. Eligibility would be determined based upon the results of the existing evaluations and the Principal Investigator will document their continued validity.

The individual obtaining informed consent will fully disclose and explain the risks and benefits of the study procedures, and answer the patient's questions about the study and the material presented in the informed consent form. Alternatives to study participation will be discussed, and the voluntary nature of participation in the study will be emphasized. This consent discussion will be documented in a consent note placed in the patient's chart.

Indicate which of the following are employed as a part of screening or main study consent procedures
✓ Consent Form

Justification for Waiver or Alteration of Consent

Waiver of consent is requested for the following
A phone screen will be used for this study. Eligibility screening for this study will be conducted under this IRB protocol.
Explain why your research can not be practicably carried out without the waiver or alteration
Dr. Moreno will screen patients on the phone before first visit to NYSPI.
Describe whether and how subjects will be provided with additional pertinent information after participation

Patients will receive additional information if requested. Results of clinical assessments and a picture of patient's functional connectivity map with the subgenual region will be available.

Persons designated to discuss and document consent

Select the names of persons designated to obtain consent/assent
2
Hellerstein, David, MD
Moreno-Ortega, Marta, PHD
Type in the name(s) not found in the above list

Study Procedures

Describe the procedures required for this study

Eligibility screening may be conducted under
WIRB Protocol #20141643, "Cognitive Changes During Treatment with TMS for Major Depression", Tarique Perera, MD, Principal Investigator; or
NYSPI IRB Protocol #6669R, "Evaluation of Potential Participants for Depression Evaluation Service (DES) Research", Jonathan Stewart, MD, Principal Investigator
If participants were enrolled in either of these studies and the screening evaluations were conducted within the prior six months, copies of all screening instruments will be made and reviewed by the study Principal Investigator. Eligibility would be determined based upon the results of the existing evaluations and the Principal Investigator will document their continued validity.

This protocol will recruit subjects from an ongoing study of rTMS treatment of depression being conducted by Dr. Tarique Perera who is a non-Columbia physician, and already approved by an independent IRB (WIRB protocol #20141643 entitled: "Cognitive Changes During Treatment with TMS for Major Depression", see attachment).

At NYSPI or at CBIC (Citigroup Biomedical Imaging Center at Weill Cornell Medical College) MRI facility all patients will come to have a brief conversation with Dr. Moreno to verify eligibility to participate in this study, and to complete fMRI scans. **Clinical assessments pre/post TMS treatments will be implemented at Contemporary Care or NYSPI.** Patients will complete some assessments using StudyTrax.

Group 1 are patients coming from Dr. Perera's offices who will be scanned at the NYSPI or CBIC MRI Unit pre/post TMS treatments. TMS treatments for this group will be implemented under Dr. Perera's protocol and WIRB. Group 2 are patients coming from Dr. Perera's offices who will come to the NYSPI or CBIC site to be scanned at the NYSPI or CBIC MRI Unit pre/post TMS treatments. **A second course of TMS will be imoplemented at any of Dr. Perera's offices (only). For both, Group 1 and Group 2, we will be doing the scanning only (at NYSPI or CBIC)** (Table 1. Timing of all Study Procedures attached). **No treatments will be implemented at NYSPI.**

Overview of Study Design:

Patients from Dr. Perera's offices will be divided in 2 groups. Group 1 (N=30) will be depressed patients undergoing standard TMS for the first time. Group 2 (N=30) constitutes those who have previously demonstrated that they do not respond to standard TMS. MDD patients prescribed to receive standard TMS for the first time (group 1) will have resting-state FMRI in order to see if we can predict their responsiveness based on the functional connectivity maps. Non-responders to standard TMS approaches (Group 2) will be randomized (3:2) to either receive targeted (N=20) or standard (N=10) repetitive TMS (rTMS) treatments. A connectivity-based targeting strategy will be used on patients undergoing targeted

rTMS to optimize target for focal brain stimulation. Response is defined as a 50% or greater reduction in starting HDRS score. Raters and patients in group 2 will be kept blinded to the treatment assignment. All patients referred from the ongoing treatment study will be assessed by 3 tesla brain MRI, MRS and CBF/CBV procedures at baseline and immediately following the final treatment. **At NYSPI we will only do the imaging component. All treatments will be implemented at any of Dr. Perea's offices.**

Patients from group 1 will be scanned at the NYSPI or CBIC MRI Unit pre/post TMS treatments. TMS treatments for this group will be implemented under Dr. Perera's protocol and WIRB. Patients from group 2, will receive another cycle of standard versus targeted TMS, 5 times a week for 6 weeks (30 treatments), followed by a taper phase of 6 sessions to cover 3 treatments in week 1, 2 treatments in week 2 and 1 treatment in week 3. For these patients, second visit to NYSPI or CBIC will occur after first cycle finishes and right before second cycle begins. Also will receive a second post-TMS scan after second cycle finishes (see Diagram 3). Patients will be classified as responders to TMS with at least 50% decrease in HDRS-24 scores from baseline. Patients will be classified as non-responders to TMS with less than 50% decrease in HDRS-24 scores from baseline.

Screening:

A phone screen will be used for this study (NT TMS Screening Phone call Script attached). Patients will come to the NYSPI to meet with Dr. Moreno to verify eligibility, and after the patient signs the informed consent form and the HIPAA authorization, will undergo clinical assessments to assure adherence to all inclusion and exclusion criteria. Eligible patients will be enrolled in the study.
Dr. Moreno will explain to patients that at NYSPI they will only come for the imaging component and that no treatments will be implemented at the NYSPI site.

MRI, MRS and CBF/CBV Scanning:

Subjects will undergo 3 tesla (3T) brain MRI-MRS-CBF/CBV scanning. None of the imaging modalities used in the study will include exogenous contrasts. MRI scans will be performed at the NYSPI or CBIC MRI facility immediately before and after the rTMS treatment. 1H MRS PRESS TE80, ASL, FSPGR, resting state MB EPI (BOLD) will be performed at 3T. Dr. Kangarlu will be responsible of Multiband EPI, PRESS and ASL for this study. To identify coordinates in the left DLPFC we will use functional connectivity (FC) seed based analysis centered on left DLPFC ROIs to identify the site (X) with peak anticorrelation with the sgACC.

DLPFC Mapping for targeted TMS (for group 2):

Targets for focal brain stimulation with repetitive TMS will be modified based on the MRI. Methodology as follow:
I. The subgenual region of interest (ROI) was constructed by placing a 5 mm radius sphere at MNI coordinates (6, 16, −10), masked to include only sampled grey matter voxels. These subgenual coordinates were chosen based on prior studies where a reduction in subgenual activity was associated with antidepressant response across a wide range of treatment modalities (Fox et al., 2012). Resting state functional connectivity across 500 healthy right-handed subjects from the Human Connectome Project data release (http://www.humanconnectome.org/data/) was used for initial analyses as an independent cohort to

construct an average group-level functional connectivity map. The entire subgenual functional connectivity map generated from this independent cohort was used as a mask to extract the average time course activation from each MDD patient.
II. Use Matlab software to generate spheres of varying radii on T1W anatomical images centered on node coordinates within the left DLPFC to account for varying focality of different potential cortical stimulation sites. This procedure will include the mapping of ROI spheres to the surface of MNI space, extract the time series courses and compute the correlation with the subgenual functional connectivity map to find the ROI with the highest anticorrelation value (X) that could serve as optimized target for focal brain stimulation. Next, we will warp the best ROI (X) into the subject native volume space for neuronavigation of TMS coil.

TMS Treatments (for group 2):

All standard TMS treatments for group 1 will be implemented at any of Dr. Perera's offices.
Second cycle of TMS treatments for group 2 will be implemented at any of Dr. Perera's offices. Subjects of this group will be randomized to either receive standard versus navigated TMS (3:2). Patients will receive a total of 36 TMS treatments, 5 times a week for the first 6 weeks (30 treatments), followed by a taper phase go 6 sessions to cover 3 treatments in week 1, 2 treatments in week 2 and 1 treatment in week 3.

Using the NeuroStar Therapy System, the subject's motor threshold (MT) will be determined and the coil placed over the left DLPFC guided by Brainsight Neuronavigation device, which uses MRI images loaded into the system to navigate the coil over the target within the DLPFC. All patients from group 2 will receive stimulation over the left DLPFC at 120% of the MT at a frequency of 10Hz; for a total of 3,000 pulses per session. A total of 36 treatment sessions will be provided over 9-weeks. **All treatments will be implemented outside the NYSPI.**

The NeuroStar TMS Therapy System is the first TMS device cleared by the U.S. Food and Drug Administration (FDA) to treat patients with Major Depressive Disorder (MDD) who have not benefited from antidepressant treatment. Treatment parameters in this study will follow FDA approval, i.e. stimulation pattern, time course, device and patient population. The "standard" procedure of coil positioning locates the left DLPFC at 5-cm anterior to the "hand motor hotspot" along the curvature of the scalp. Alternate stimulation site within the DLPFC in each patient will be used to personalize treatments based on their rsfMRI, therefore its application is considered off-label. Please find IDE Decision Worksheet in additional documents related to this study (uploads section).

Brainsight for TMS:

Brainsight is what is generally referred to as a neuronavigator (also often called a frameless stereotaxy device). Its main function is analogous to a GPS, but applied to the brain. The device takes as input, the structural MR images of the subject, and using an infrared position sensor and related accessories, maps the location and orientation of a TMS coil held on the subject's head to the images and displays a representation of the coil on the images.
This provides two important functions. First, it displays a live representation of the coil on the images on the computer screen, allowing the operator to accurate to use the MR images (and the anatomy shown by the images) to determine the location of the coil on the subject's head. Second, fMRI images may be overlaid

on the structural images. These images may be used to define a location in the brain to be stimulated and the coordinates of this target stored. While holding the coil on the head, Brainsight indicates in which director to move the coil to quickly and accurately place the coil over the target. One placed, the system monitors the coil's activity and can automatically record the coil's position and orientation w.r.t. target for quality assurance. In addition to the coil, the subject's head is also being monitored, so head movement is shown allowing immediate adjustment to the coil or head location to ensure consistent stimulation during the entire TMS session.

Dr. Roch Comeau, president of Rogue Research Inc., is a consultant in this research project to support the portions of the project related to the use of the neuronavigation system and has adapted both navigators to work with Neuronetics stimulator. Please find Dr. Comeau's Letter uploaded in additional documents related to this study (uploads section). Rogue Research, Inc. is the company responsible for neuronavigation. Dr. Roch Comeau, President of Rogue Inc, will be available to ensure procedures for neuronavigation are followed accurately. He has already come to Contemporary Care to interface the Neuronavigational device with NeuroStar TMS devices to ensure proper use of neuronavigation to guide TMS coil.

An IDE is not required for the Brainsight Neuronavigation stereotaxic device. Please find attached a letter from Dr. Comeau, who is President of Brainsight Neuronavigation company that manufactures the device.

Criteria for Early Discontinuation:

CGI-Global, HDRS-24 and C-SSRS will be assessed weekly in patients undergoing second course of TMS **at any of Dr. Perera's offices, not at NYSPI.** A licensed MD assigned to the study will meet with patients weekly and assess clinical worsening, suicidality, and intolerable side effects. If patients show a worsening of their general psychopathological condition with 50% increase in HDRS-24 scores from baseline on 2 consecutive ratings or any occurrence of a CGI-I score of 6 or 7 will trigger a clinical evaluation and then a clinical judgment as to wether the patient should be discontinued. Such evaluations will be documented in the patient's chart at **Contemporary Care**. If patients miss any three consecutive treatment sessions or any five treatment sessions, they will be dropped from the study, and after treatment recommendations they will be returned to routine clinical management under the supervision of Dr. Perera.

In case patients appear to be at increased risk for suicide, he/she will be dropped from the study and accompanied to the ER for evaluation. Additionally, intolerable side effects or any medical worsening will result in immediate withdrawal from the study. All patients dropped out from the study will be returned to routine clinical management under the supervision of Dr. Perera.

Review for any incidental findings on MRI:

In adherence to the revised Incidental Findings Policy for neuroimaging done at Columbia as described in the 3/27/15 memo from the CUMC IRB, MRI research scans will be read by credentialed neuroradiologists within 2 weeks. The subject or his or her individual physician will be contacted by letter with information about their MRI research scan.

You can upload charts or diagrams if any

Criteria for Early Discontinuation

Criteria for Early Discontinuation

CGI-Global, HDRS-24 and C-SSRS will be assessed weekly in patients undergoing second course of TMS at **any of Dr. Perera's offices, not at NYSPI**. A licensed MD assigned to the study will meet with patients weekly and assess clinical worsening, suicidality, and intolerable side effects. If patients show a worsening of their general psychopathological condition with 50% increase in HDRS-24 scores from baseline on 2 consecutive ratings or any occurrence of a CGI-I score of 6 or 7 will trigger a clinical evaluation and then a clinical judgment as to wether the patient should be discontinued. Such evaluations will be documented in the patient's chart at **Contemporary Care.** If patients miss any three consecutive treatment sessions or any five treatment sessions, they will be dropped from the study, and after treatment recommendations they will be returned to routine clinical management under the supervision of Dr. Perera or their referring psychiatrist.

In case patients appear to be at increased risk for suicide, he/she will be dropped from the study and accompanied to the ER for evaluation. Additionally, intolerable side effects or any medical worsening will result in immediate withdrawal from the study. All patients dropped out from the study will be returned to routine clinical management under the supervision of Dr. Perera or their referring psychiatrist.

Blood and other Biological Samples

Please create or insert a table describing the proposed collection of blood or other biological specimens
Not applied.

Assessment Instruments

Create a table or give a brief description of the instruments that will be used for assessment
Depressed Patients:
Assessments, including SCID and HRSD will be performed as part of the referring protocol, as listed below. No independent assessments will be performed as part of the present study.
Dr. Tarique Perera, WIRB protocol #20141643 entitled: "Cognitive Changes During Treatment with TMS for Major Depression", see attachment.

Clinical Assessments at the NYSPI site will include:
1. Interview for DSM-IV-TR Disorders (SCID-IV-TR). SCID, DSM-IV-TR
2. HRSD28-MADRS Interview
3. HDRS-24
4. CGI-Global
5. C-SSRS
6. The Dimensional Anhedonia Rating Scale (DARS)

7. The Ruminative Responses Scale (RRS)
8. The Selective Reminding Test (SRT)
9. The Digit Symbol Substitution Test (DSST)
10. Speech Recognition Threshold (SRT)
11. The Controlled Oral Word Association Test (COWAT)

Please find Table 2. Clinical Assessments attached.

Please attach copies, unless standard instruments are used

Off label and investigational use of drugs/devices

Choose from the following that will be applicable to your study
✓ Device

Off label and investigational use of devices

Device #1

Name of the device
NeuroStar TMS Therapy System
Manufacturer and other information
NeuroStar TMS Therapy System, Neuronetics Inc.

The NeuroStar TMS Therapy System is the first TMS device cleared by the U.S. Food and Drug Administration (FDA) to treat patients with Major Depressive Disorder (MDD) who have not benefited from antidepressant treatment. Treatment parameters in this study will follow FDA approval, i.e. stimulation pattern, time course, device and patient population. The "standard" procedure of coil positioning locates the left DLPFC at 5-cm anterior to the "hand motor hotspot" along the curvature of the scalp. Alternate stimulation site within the DLPFC in each patient will be used to personalize treatments based on their tfMRI, therefore its application is considered off-label.
Approval Status
No IDE is required
Choose one of the folowing options
Device is 'Non-significant risk'
Explain

The "standard" procedure of positions the coil on the left DLPFC at 5-cm anterior to the "hand motor hotspot" along the curvature of the scalp (4, 8-11). However, this technique misses the DLPFC (6, 7) more than 1/3 of the times, since it does not account for differences in skull size or variations in prefrontal anatomy relative to motor cortex location.

We have designed a functional connectivity-based targeting strategy (NT TMS) that allows us to select the target within DLPFC with much higher accuracy to assure individualized target location. This strategy is based upon the hypothesis that the clinical efficacy of rTMS depends on the FC between left DLPFC and remote regions such as the sgACC, and that the precise regions of DLPFC that are functionally connected to sgACC may differ across individuals. Thus, individualized FC patterns using standard rsFMRI FC measures offers the target for engagement of TMS across individuals more precisely. Such new targeting (NT) strategy for TMS is a novel intervention backed up by strong evidence from the scientific community and well-supported theoretical rationale that is ready for early-phase testing. Our proposed NT TMS has a high potential to reduce the burden of depression by precisely aiming the intervention to the sites directly involved in the networks known to be faulty in the brain of MDD patients.

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Device #2

Name of the device
Brainsight TMS Neuronavigation
Manufacturer and other information

Rogue Research, Inc is themanufacturer.
Brainsight coordinate measurement device is designed for TMS applications.

Approval Status
No IDE is required
Choose one of the following options
Device is 'Non-significant risk'

Explain

Brainsight Neuronavigation enables the TMS coil to be positioned over a specific target location based upon individual's MRI image. Brainsight does not provide any diagnostic or therapeutic information for TMS.

We have spoken to the company and their understanding is that an IDE is not required. Please find attached a letter from Dr. Comeau in the uploads section of the PSF, who is President of Brainsight Neuronavigation company that manufactures the device. His understanding is that there are already other Brainsight devices at Columbia that are being used without IDE.

Research Related Delay to Treatment

Will research procedures result in a delay to treatment?
Yes
Maximum duration of delay to any treatment
No treatment is provided at NYSPI. Participation in this protocol may result in a brief (1 week)

delay in treatment implementation by Dr. Perera in order to allow time for the fMRI mapping for targeted rTMS to be performed (see Study procedures).
Maximum duration of delay to standard care or treatment of known efficacy
1 week
Treatment to be provided at the end of the study
Patients who do not respond to standard rTMS will be offered individualized targeting rTMS as part of their ongoing care, **outside the NYSPI. No treatment is provided at NYSPI.**

Clinical Treatment Alternatives

Clinical treatment alternatives
There are non-drug and drug therapies available to treat depression. Depression is often initially treated with psychotherapy (talk therapy) and antidepressant medication administered together. Although antidepressants can be effective for some patients, they do not work for everybody. Additionally, antidepressants often result in unwanted side effects.
Many patients do not receive adequate benefit from antidepressant medication and/or cannot tolerate the side effects caused by them. For these patients, alternative treatments that involve the use of a medical device are available. These treatments include transcranial magnetic stimulation (TMS), electroconvulsive therapy (ECT) and vagus nerve stimulation (VNS).

Dr. Moreno will discuss all other alternative treatments for depression with patients before the second course of TMS in group 2, including antidepressant medications, psychotherapy, electroconvulsive therapy (ECT) and vagus nerve stimulation (VNS).

No treatment is provided at NYSPI.

Risks/Discomforts/Inconveniences

Risks that could be encountered during the study period

Participants could become anxious, bored or tired while participating in medical or psychiatric screening

MRI
While there have been no reports of any harmful long-term effects caused by MRI magnets of the same or even higher strength as those used in this study, the long-term effects of being placed in a magnet are unknown. Although there are no risks associated with pregnancy, we will not scan anyone who is pregnant. Females in their childbearing years will be asked to take a pregnancy test for exclusion. Sometimes sensations such as tingling or twitching are experienced, which are caused by the magnetic field that can stimulate peripheral nerves. Exclusion criteria for the scan include pacemakers and other metallic implants, which would pose a risk to the subject if s/he were exposed to strong magnetic fields. It may be uncomfortable to lie motionless in the MRI camera and it may cause some subjects to feel anxious and

claustrophobic. Normal operation of the MR system produces loud noises, and foam earplugs will be provided to reduce the noise. Our staff will be available to provide support, reduce anxiety, optimize the comfort of the subject and remove the subject from the scanner if requested. There are no known long-term risks from magnetic resonance imaging studies. An acute risk of burns to the skin is presented by medicinal skin patches, and subjects will be asked to remove patches before entering the scanner. Short-term risks also include tissue heating from excessive systemically absorbed radiofrequency radiation and stimulation of peripheral nerves from rapidly changing magnetic fields. Both software and hardware protection schemes are present in the equipment to prevent excessive amounts or rates of change of systemically absorbed radiofrequency radiation. At 3T, short-term side effects include mild dizziness, nausea, and metallic taste. These effects are due to movement within the magnetic field and are terminated when subjects cease head movement. The scanner to be used in this study (at NYSPI) is a non significant risk device.

NeuroStar NT TMS Therapy
Seizures: In clinical trials using the NeuroStar Therapy System, which included over 10,000 TMS treatments, no seizures were reported. The current device labeling warns that the expected and observed frequency and - occurrence of seizures is less than 1 in 30,000 treatments (<0.003%) and 1 in 1000 patients (<0.1%). Rare cases have reported the development of seizures during or immediately after transcranial magnetic stimulation (TMS). Having a seizure includes a potential effect on your future employability, insurability, and ability to drive. Should you experience a seizure that is related to magnetic stimulation, your doctor will provide you with a letter stating that the seizure was produced under experimental conditions and that there is no reason to expect another occurrence. Individuals who have a history of seizures or have been diagnosed with epilepsy will be excluded from this research study.

Muscle Twitching: You may feel twitches in the muscles of your face during the magnetic stimulation.

Headache: A mild headache can occur following TMS treatment that usually resolves soon after the procedure. The headaches may be from maintaining a fixed head position for the duration of the TMS treatment. We will try to reduce the risk of headache by assuring your comfort before and during the procedures.

Changes in hearing: The loud “click” produced by the TMS stimulator can cause temporary hearing changes following treatment. This is prevented by wearing soft foam earplugs during treatment.

Low blood pressure and feelings of nausea: If you take blood pressure medications you may have a low blood pressure while sitting restfully in the research chair. Some may also have a feeling of nausea. Eating and taking fluid before the session will help prevent these symptoms. If these symptoms occur, the session will be stopped and resumed only when the symptoms resolve.

Also, metal objects located close to the hand held TMS coil might move during magnetic stimulation. These items should be removed during treatment. Individuals with any metal implants will also be excluded from the research study.

All efforts will be made to minimize these risks by using only trained personnel who are experienced and skilled in using the device. Moreover, all TMS sessions will be performed in a medical setting with access

to a skilled medical team and life-support equipment. **All TMS treatments will be implemented outside the NYSPI site.**

NT TMS is an investigational treatment which is not approved by the FDA. A licensed MD assigned to the study **at any of Dr. Perera's offices** will meet with patients weekly and assess clinical worsening, suicidality, and intolerable side effects. **No NT TMS will be implemented at the NYSPI site.** If patients show a worsening of their general psychopathological condition, a clinical judgment after correspondent clinical evaluation will be made as to whether NT TMS treatments should be discontinued. If patients miss any three consecutive treatment sessions or any five treatment sessions, they will be dropped from the study, and after treatment recommendations they will be returned to routine clinical management under the supervision of Dr. Perera.

TMS Neuronavigation System
There are no anticipated risks to you from the neuronavigator. Neuronavigation systems enable accurate planning, targeting and monitoring for brain stimulation studies using TMS.

Describe procedures for minimizing risks
See above

Methods to Protect Confidentiality

Describe methods to protect confidentiality

All data (written and electronic) will be coded by number. A master list identifying subjects with codes will be kept under lock and key, separate from any research records or the computer database, with access restricted to research staff, to the extent permitted by law. Only staff directly involved in this project will have access to the master list linking subject names to code numbers. In the informed consent form, subjects are told that the information they provide and all findings of testing will be kept strictly confidential, with access limited to the research staff, and possibly state or federal regulatory personnel. Information about the patients' condition and treatment will be kept in a computer but the patients' names will not appear in this database. The information will only be linked to a code number assigned for the purposed of maintaining privacy. Only members of the research team will have access to the computer.

If a medical event occurs involving the NeuroStar TMS, Neuronetics, the manufacturer of the NeuroStar, may need to see confidential information as it relates to the event.

Will the study be conducted under a certificate of confidentiality?
No

Direct Benefits to Subjects

Direct Benefits to Subjects

There are no direct benefits to participants.

Individualized targeting of rTMS for Non-responders to standard TMS approaches (Group 2) may improve treatment response.

Compensation and/or Reimbursement

Will compensation or reimbursement for expenses be offered to subjects?
No

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Uploads

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Upload any additional documents that may be related to this study
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NEW YORK STATE PSYCHIATRIC INSTITUTE
Informed Consent for Participation in Research

MRI Scanning Consent Form

TITLE OF STUDY: Neuroimaging in Patients Undergoing TMS for Depression

PRINCIPAL INVESTIGATOR: Marta Moreno-Ortega, PhD

AFFILIATION: Columbia University, New York State Psychiatric Institute

KEY ELEMENTS

Little is known about neither how depression affects the brain while people are in a resting state (i.e. not doing anything) nor what brain changes result from receiving rTMS treatment. We are asking you to have an MRI of your brain before you start your rTMS treatment sessions, as well as after your daily treatment sessions are completed. This will be done with a special kind of MRI, called a functional MRI (fMRI), which can measure how active your brain is while you are resting in the machine. We will ask you to do so regardless of you receive benefit from your TMS treatment or not. We will use the data we collect to better understand how depression and TMS affect the brain, both with and without depressive symptom improvement.

The purpose of this form is for you to fully understand what the study involves, and then decide if you want to participate.

PURPOSE OF THE STUDY

You are being asked to participate in this study because you have elected to receive repetitive transcranial magnetic stimulation (rTMS) as a means to treat your depression. While rTMS has demonstrated antidepressant effects, it has been underutilized to date, as there is a wide variety in patients' responses to treatment: some people who receive TMS have a marked improvement in the symptoms of their depression while others receive no benefit. It is unclear why this happens. However, we know that one factor which affects treatment response is the accuracy of where the TMS coil is placed during the treatment sessions. Differences in brain structure and function between people make it important to have each session's location be targeted specifically for the individual. One way this can be achieved is by using magnetic resonance imaging (MRI), which is a way of taking pictures of the brain. With images of one person's brain, a specific part of the standard rTMS treatment region can be located, and this information can be used to ensure accurate coil placement and targeting. In this study, we will examine methods by which MRI can be used to individualize rTMS treatments by identifying an optimal stimulation site for each person, which we believe may have the potential to increase the efficacy of the treatment. As part of this study you will be asked to come to the **NYSPI or CBIC (Citigroup Biomedical Imaging Center at Weill Cornell Medical College)** to have an MRI scan of your brain pre/post TMS treatments.

VOLUNTARY NATURE OF RESEARCH

Participation in this research study is voluntary. If you decide not to participate, or if you later decide to stop participating, you will not lose any benefits to which you are otherwise entitled. A decision not to participate or withdraw your participation will not affect your current or future treatment at the New York State Psychiatric Institute or Columbia University.

ALTERNATIVES TO PARTICIPATION

This is not a treatment study. Information being collected is for research purposes only and is to learn more about how depression affects the brain, not about you. It is not necessary to participate in this research study to have an MRI, and the MRI done as part of this study is not the same as one done for medical purposes.

STUDY PROCEDURES

At NYSPI you will only come to have a brief conversation with Dr. Moreno to verify you are eligible to participate in this study and to have a clinical/neurocognitive evaluation with a member of our staff. **To complete your fMRI scans you will come to NYSPI or CBIC. No TMS treatments will be implemented at the NYSPI site.**

Evaluation and Screening

After you have signed this consent form that you want to participate in this study, you will be evaluated to see if you are eligible to participate and complete the study procedures. You will meet with a member of our staff, and you will be asked about your current and past physical and mental health. You will be asked to fill out some forms requesting basic demographic information, what hand you use to do certain tasks, and to see if it is safe for you to have an MRI, which asks you about any metal you may have or have had in your body. If you are a woman of child bearing age, you will be asked to provide a urine sample for a pregnancy test. This should take about half an hour. It is possible that, after completing the evaluation, you might not be eligible to be a study participant. If so, you will not complete any further testing or assessments. After the evaluation is completed and you are deemed eligible to participate, there will be two testing sessions, which will occur on different days: one session to complete pre-treatment fMRI and one to do the post-treatment fMRI. These are described in detail below. In the Study Itinerary section, a concise timeline of exactly what procedures you will undergo and when these procedures will occur are described.

Functional Magnetic Resonance Imaging (fMRI)

You will be asked to have an MRI scan before your first TMS treatment and within a few days after your last treatment. The MRI uses strong magnetic fields and radio waves to take pictures of your brain. In this study, your brain will be the only body part that is imaged. The scan we are performing is called a functional magnetic resonance imaging scan (fMRI). It is different from a regular MRI in that the images we get from the scan will show how active your brain is while you are at rest (i.e. not doing anything). For you, this will be like any other type of MRI you may have had in the past. Before beginning the imaging procedure, we will determine that you do not have a pacemaker or any unsafe metallic implants, such as an aneurysm clip, artificial heart valve, or certain tattoos. You must also inform us if you have any metal objects inside your body, since some of these objects may prevent you from having an MRI. You will then be asked to remove any medicinal patches on your skin and any metal or magnetized objects (such as keys, chains, jewelry, retainers, medication patches, hairpins, credit cards) that you may have on you.

MRI involves lying on a table that slides into a large magnet shaped like a cylinder, and you will then be asked to stay awake and lie motionless on the table for the duration of the scan. You will not feel anything, but you will hear a knocking noise. This is a normal sound produced by the MRI scanner and does not indicate that anything is wrong. You will be given foam earplugs to reduce this noise. You will not be able to see out of the MRI machine, but you will be able to hear us and be heard if you wish to say anything. The MRI technician and other staff will be in the control room next-door the whole time. Each scan will last about one hour. You may stop the scan at any time.

While MRI scans are sometimes done for clinical purposes, the kind of MRI scan you will have as part of this study is for research purposes only. This means that the scans are not designed to provide clinical

information that might be helpful to you or your doctor, and they may not show problems that would normally be found in an MRI ordered to evaluate a specific medical problem. It is likely that the MRI scan will not have the quality of those done for clinical purposes. The results of your scan will be maintained in an electronically secure database **at NYSPI or CBIC**. and is accessible solely to the members of the research team. However, within a month of the MRI, the scan will be read by a neuroradiologist for evidence of any obvious irregularities requiring follow-up. You, or a physician whom you may choose, will be informed only when significant abnormalities are detected. If you wish, we can also inform you if there were no obvious findings. Given the nature of the scan, the absence of a finding does not mean that one is not present. The MRI session should take 1 hour.

Clinical Assessments

You will be asked to have an assessment session before your first TMS treatment and within a few days after your last treatment, scheduled for the same day you come to the **NYSPI or CBIC** to have your MRI scan. The testing session will include questions regarding your depressive symptoms and tasks related to memory and other cognitive capabilities. The results of your testing session will be maintained in an electronically secure database at NYSPI and is accessible solely to the members of the research team. The testing session should take about two hours and will be implemented after your MRI scan.

Study Itinerary

Day 1: You will come to the NYSPI prior to your first TMS treatment to meet with Dr. Moreno and a member of her research staff to complete a screening session to verify eligibility, and to have your Clinical Assessments session. You will come to the **NYSPI or CBIC** to have your MRI scan.

You will be first screened, then a member of the research staff will meet with you in the testing room for your Clinical Assessments session, and when the Clinical Assessments session finishes, you will have your MRI scan. The entire visit should take 3 to 5 hours depending on the MRI site.

Day two: You will come to the NYSPI after your TMS treatments are completed to meet with Dr. Moreno and a member of her research staff to have your Clinical Assessments session and MRI scan. Procedures will follow same regimen as in day 1.

RISKS AND INCONVENIENCES

Evaluation and Assessments

There are no anticipated risks to you from the clinical and medical evaluations. You may find the interviews about your physical or psychological health upsetting, but no more so than you would undergo as part of your routine health care. If you do, you can decide not to answer specific questions, ask for a break, or stop the interview.

MRI

The long-term effects of being placed in a magnet of this strength (3 Tesla) are unknown, but you should be aware that there have been no reports of any ill long-term effects caused by magnets of the same or even higher strength, either here or elsewhere. Also, although there are no known risks associated with pregnancy, we will not scan someone who is pregnant. Therefore, you should understand that if you are a woman in your child-bearing years, pregnancy testing will be used to assure that you are not pregnant.

Some people have reported sensations during the MRI scan, 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. If you experience sensations and feel that these are uncomfortable, you can tell the MR technologist, and he or she will stop the scan immediately. Occasionally, some people experience nervousness or claustrophobic feelings due to the scanner's small space. If you encounter any discomfort, you can tell the MR technologist, and he or she will stop the scan immediately. Despite these experiences, no one has ever had sensations from the scanning that did not stop as soon as the scanning stopped.

Except for pacemakers and some types of metallic implants, we know of no health hazard from the MRI scan. The MRI scan is not painful, but lying still on the scanning table may be slightly uncomfortable.

POTENTIAL BENEFIT TO YOU OR TO OTHERS

You are not expected to benefit from participation in this study.

CONFIDENTIALITY

Any information obtained during this study and identified with you will remain confidential. **Your private information or MRI could be used for future research studies or distributed to another investigator for future research studies, without identifiers.**

Records will be available to research staff, and to Federal, State, and Institutional regulatory personnel (who may review records as part of routine audits). All information will be stored in locked files and will be kept confidential to the extent permitted by law.

All data (written and electronic) will be coded. A master list matching the subject with codes will be kept under lock and key, which is separate from any research records or the computer database. Access is restricted to research staff, to the extent permitted by law. Only staff directly involved in this project will have access to the master list linking your name to code numbers. Your name and other personal identifying information will be stored in files and in an electronically secure database at the New York State Psychiatric Institute.

Your MRI will be interpreted and the results will be shared with you or a physician who you may designate. Your MRI report will be maintained as part of the (electronically secured) clinical database at the New York State Psychiatric Institute along with your name and will be accessible to members of the research team. Your psychiatric diagnosis will not be a part of the report.

You should know that if we learn that you or someone else is threatened with serious harm, such as a child or an elderly person being abused, the investigators would take actions to protect you and others, including reporting these situations to proper authorities.

Clinically relevant research results will not be disclosed to participants.

COSTS AND COMPENSATION

There is no cost to participate in this study. You will not be paid to participate in this study.

IN CASE OF INJURY

Federal regulations require that we inform participants about our institution's policy with regard to compensation and payment for treatment of research-related injuries. If you believe that you have sustained an injury as a result of participating in a research study, you may contact the Principal Investigator, Dr. Marta Moreno-Ortega, at (914) 218-7311 so that you can review the matter and identify the medical resources that may be available to you.

In case of injury, New York State Psychiatric Institute will provide short term emergency medical treatment, which has been determined to be necessary by New York State Psychiatric Institute's doctors, and which is within the capability of New York State Psychiatric Institute to provide. In addition, we will provide assistance in arranging follow up care in such instances.

New York State Psychiatric Institute and Research Foundation for Mental Hygiene do not provide compensation or payment for treatment of research related injuries. However, you should be aware that you do not give up your legal right to seek such compensation through the court by participating in this research.

QUESTIONS

Dr. Moreno-Ortega, or her research team, will answer, to the best of their ability, any questions that you may have now or in the future about the research procedures or about your response to the procedures. You may call Dr. Moreno-Ortega at (914) 218-7311. You will be given the opportunity to discuss in confidence any questions you may have. You will be given a copy of this consent form to keep.

If you have any questions about your rights as a research participant, want to provide feedback, or have a complaint, you may call the NYSPI Institutional Review Board (IRB). (An IRB is a committee that protects the rights of human subjects in research studies). You may call the IRB Office at (646) 774-7155 during regular office hours.

DOCUMENTATION OF CONSENT

☐ Please check this box if you would like to be informed of your MRI results, even if there were no obvious irregularities detected

☐ By checking this box, I agree that the researchers may contact me in the future to determine if I am interested in participating in further studies. Participation in any subsequent study is optional.

I voluntarily agree to participate in the research study described above.

Signature of participant _____ Date_____

Printed name of participant _____

I have discussed the proposed research with this participant including the risks, benefits, and alternatives to participation (including the alternative of not participating in the research). The participant has had an opportunity to ask questions and, in my opinion, is capable of freely consenting to participate in this research.

Signature_____ Date_____

Printed name_____

Subject Name: _____

Thank you for participating in our study. We remind you that the MRI scan of the brain that we performed was for research purposes only. It would not show problems that would be picked up by a more specialized medical MRI scan ordered by your doctor for a specific medical problem. The scan provides little clinical information other than the presence or absence of certain irregularities. In fact, the absence of a finding does not mean that one is not present.

The review of your scan was done by a doctor trained in brain MRI interpretation (a neuroradiologist) who found **no obvious irregularities** during the reading of the MRI. If you would like to request that a copy of the report be sent to your physician, please call Dr. Moreno-Ortega at 914-218-7311.

Please contact us if you have any questions.

Sincerely,

Dr. Moreno-Ortega

Subject Name: _____

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As we mentioned in our recent telephone conversation, the review of your scan by a doctor trained in brain MRI interpretation (a neuroradiologist) showed **an irregularity,** and we recommend that you follow up with your physician as soon as possible to determine if any further action is necessary. If you would like to request that a copy of the report be sent to your physician, please call Dr. Moreno-Ortega at 914-218-7311.

Please contact us if you have any questions.

Sincerely,

Dr. Moreno-Ortega

NEW YORK STATE PSYCHIATRIC INSTITUTE
Informed Consent for Participation in Research

MRI Scanning Consent Form

TITLE OF STUDY: Neuroimaging in Patients Undergoing TMS for Depression

PRINCIPAL INVESTIGATOR: Marta Moreno-Ortega, PhD

AFFILIATION: Columbia University, New York State Psychiatric Institute

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body. If you experience sensations and feel that these are uncomfortable, you can tell the MR technologist, and he or she will stop the scan immediately. Occasionally, some people experience nervousness or claustrophobic feelings due to the scanner's small space. If you encounter any discomfort, you can tell the MR technologist, and he or she will stop the scan immediately. Despite these experiences, no one has ever had sensations from the scanning that did not stop as soon as the scanning stopped.

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CONFIDENTIALITY

Any information obtained during this study and identified with you will remain confidential. Your private information or MRI could be used for future research studies or distributed to another investigator for future research studies, without identifiers.

Records will be available to research staff, and to Federal, State, and Institutional regulatory personnel (who may review records as part of routine audits). All information will be stored in locked files and will be kept confidential to the extent permitted by law.

All data (written and electronic) will be coded. A master list matching the subject with codes will be kept under lock and key, which is separate from any research records or the computer database. Access is restricted to research staff, to the extent permitted by law. Only staff directly involved in this project will have access to the master list linking your name to code numbers. Your name and other personal identifying information will be stored in files and in an electronically secure database at the New York State Psychiatric Institute.

Your MRI will be interpreted and the results will be shared with you or a physician who you may designate. Your MRI report will be maintained as part of the (electronically secured) clinical database at the New York State Psychiatric Institute along with your name and will be accessible to members of the research team. Your psychiatric diagnosis will not be a part of the report.

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Clinically relevant research results will not be disclosed to participants.

COSTS AND COMPENSATION

There is no cost to participate in this study. You will not be paid to participate in this study.

IN CASE OF INJURY

Federal regulations require that we inform participants about our institution's policy with regard to compensation and payment for treatment of research-related injuries. If you believe that you have sustained an injury as a result of participating in a research study, you may contact the Principal Investigator, Dr. Marta Moreno-Ortega, at (914) 218-7311 so that you can review the matter and identify the medical resources that may be available to you.

In case of injury, New York State Psychiatric Institute will provide short term emergency medical treatment, which has been determined to be necessary by New York State Psychiatric Institute's doctors, and which is within the capability of New York State Psychiatric Institute to provide. In addition, we will provide assistance in arranging follow up care in such instances.

New York State Psychiatric Institute and Research Foundation for Mental Hygiene do not provide compensation or payment for treatment of research related injuries. However, you should be aware that you do not give up your legal right to seek such compensation through the court by participating in this research.

QUESTIONS

Dr. Moreno-Ortega, or her research team, will answer, to the best of their ability, any questions that you may have now or in the future about the research procedures or about your response to the procedures. You may call Dr. Moreno-Ortega at (914) 218-7311. You will be given the opportunity to discuss in confidence any questions you may have. You will be given a copy of this consent form to keep.

If you have any questions about your rights as a research participant, want to provide feedback, or have a complaint, you may call the NYSPI Institutional Review Board (IRB). (An IRB is a committee that protects the rights of human subjects in research studies). You may call the IRB Office at (646) 774-7155 during regular office hours.

DOCUMENTATION OF CONSENT

☐ Please check this box if you would like to be informed of your MRI results, even if there were no obvious irregularities detected

☐ By checking this box, I agree that the researchers may contact me in the future to determine if I am interested in participating in further studies. Participation in any subsequent study is optional.

I voluntarily agree to participate in the research study described above.

Signature of participant _____ Date_____

Printed name of participant _____

I have discussed the proposed research with this participant including the risks, benefits, and alternatives to participation (including the alternative of not participating in the research). The participant has had an opportunity to ask questions and, in my opinion, is capable of freely consenting to participate in this research.

Signature_____ Date_____

Printed name_____

New York State Psychiatric Institute (NYSPI)
Authorization to Use or Disclose Health Information during a Research Study

Protocol Number: 7159 **Principal Investigator:** Marta Moreno-Ortega, PHD

Name of Study: Neuroimaging in patients undergoing TMS for depression

Before researchers can use or share any identifiable health information ("Health Information") about you as part of the above study (the "Research"), the New York State Psychiatric Institute (NYSPI) is required to obtain your authorization. You agree to allow the following individuals and entities to use and disclose Health Information about you as described below:

- New York State Psychiatric Institute (NYSPI), your doctors and other health care providers, if any, and
- The Principal Investigator and his/her staff (together "Researchers"). Researchers may include staff of NYSPI, the New York State Office of Mental Health (OMH), Research Foundation for Mental Hygiene, Inc. (RFMH), and Columbia University (CU), provided such staff is a part of the study, and
- Providers of services for the Research at CU, NYSPI and/or RFMH, such as MRI or PET, or Central Reference Laboratories (NKI), if indicated in the consent form**.**

1. The Health Information that may be used and/or disclosed for this Research includes:

☑ All information collected during the Research as told to you in the Informed Consent Form.
☑ Health Information in your clinical research record which includes the results of physical exams, medical and psychiatric history, laboratory or diagnostic tests, or Health Information relating to a particular condition that is related to the Research.
☐ Additional information may include:

2. **The Health Information listed above may be disclosed to:**

☑ Researchers and their staff at the following organizations involved with this Research:
Contemporary Care; Mount Sinai; Citigroup Biomedical Imaging Center at Weill Cornell Medical College

☐ The Sponsor of the Research,

and its agents and contractors (together, "Sponsor"); and
☑ Representatives of regulatory and government agencies, institutional review boards, representatives of the Researchers and their institutions to the level needed to carry out their responsibilities related to the conduct of the research.
☑ Private laboratories and other persons and organizations that analyze your health information in connection with this study

☐ Other (family members or significant others, study buddies, outside agencies etc.) Specify:

3. By giving permission to release your Health Information as described above, you understand that your Health Information may be disclosed to individuals or entities which are not required to comply with the federal and state privacy laws which govern the use and disclosure of personal Health Information by NYSPI. This means that once your Health

Information has been disclosed to a third party which does not have to follow these laws (e.g., a drug company or the Sponsor of the Research), it may no longer be protected under the HIPAA or NYS Mental Hygiene Law requirements but is subject to the terms of the consent form and may be subject to other state or federal privacy laws or regulations.

4. Please note that:

- You do not have to sign this Authorization form, but if you do not, you may not be able to participate in the study or receive study related care. You may change your mind at any time and for any reason. If you do so, you may no longer be allowed to participate in the study. If you withdraw this Authorization the research staff and the Sponsor, if this is sponsored research, may still use or disclose Health Information containing identifying information they already have collected about you as needed to maintain the reliability of the research. Any request to withdraw this Authorization must be made in writing to (enter name and contact information below):

  Marta Moreno-Ortega. 1051 Riverside Dr., Unit 21. New York, NY 10032.
  (p): (914)218-7311 (f): (646) 774-5428

- While the Research is going on, you may not be allowed to review the Health Information in your clinical research record that has been created or collected by NYSPI. When this research has been completed you may be allowed to see this information. If it is needed for your care, your Health Information will be given to you or your Doctor.

5. This Authorization does not have an end date.

6. You will be given a copy of this form after you have signed it.

I agree to the use and disclosure of Health Information about me as described above:

_____ _____

Signature of Participant/ Legal Representative Date

_____

Printed Name of Participant

_____

Relationship of Legal Representative to Participant (if applicable)

We also ask you or your legal representative to initial the statements below:

☐ **I have received a copy of the NYSPI/OMH Notice of Privacy Practices.**