Brain Imaging of rTMS Treatment for Depression
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1. PURPOSE OF THE STUDY

a. Brief Summary

The overarching goal of this research program is to elucidate causal and directional neural network-level abnormalities in depression, and how they are modulated by an individually-tailored, circuit-directed intervention.

b. Objectives

To examine the impact of antidepressant rTMS on causal network abnormalities in depression, and the relationship between baseline networks deficits and clinical outcome.

c. Rationale for Research in Humans

This is a study of Major Depressive Disorder in humans.

2. STUDY PROCEDURES

a. Procedures

All eligible subjects will undergo structured diagnostic interviews, including a MDD-specific assessment at Stanford shortly after recruitment. Subjects will then have a pre-treatment baseline MRI session (structural, resting), a concurrent fMRI/TMS scan session and a concurrent EEG/TMS session within two weeks at one of the Stanford scan sites. Preparation for physiological measurements will take 30-40 minutes including calibration time. These initial assessments provide a baseline for comparing pre- to post-treatment brain changes in patients. In the case of the baseline assessments, TMS is a probe for testing brain circuitry and as such, actual TMS must be used. All participants, whether randomized to active or sham, complete the TMS baseline assessments in order to provide baseline brain activation profiles.

After determining study eligibility, participants will wear an EEG cap which is like a swimming cap with Ag/AgCl electrodes which will be filled with gels through syringe. The Ag/AgCl electrodes for EOG.

Subjects will then be randomized to receive 4 weeks daily rTMS vs. sham (placebo) treatment sessions (total 20). For participants who receive sham (placebo) treatment for the first 4 weeks, they are offered 4 weeks of open-label active treatment. For participants who receive active

treatment during the first 4 weeks of treatment, they are not offered another 4 weeks of treatment.

Finally, another fMRI/TMS scan and EEG/TMS session will be scheduled within one week post rTMS treatment. Depression and anxiety will be evaluated using MDD and anxiety specific assessment pre and post- rTMS/sham treatment and after the 10th and 20th (and 30th and 40th for open-label patients) treatment session during rTMS/sham.

Patients who drop out of treatment will be encouraged to return for clinical and imaging assessments. Participants who continue onto the open-label treatment will also come in for another fMRI/TMS scan and EEG/TMS session within 1 week after their second 4 weeks of treatment.

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b. Procedure Risks

The experiment will terminate at the conclusion of the TMS stimulation and fMRI data acquisition or at any point that a subject requests to terminate the experiment. In addition, if the subject does not respond to questioning about their well-being during the experiment, the experiment will be terminated. If the experiment must be terminated for any reason that requires acute medical intervention, EMS will be immediately notified and directed to the 3T scanner location by the experimenters.

MRI/fMRI

Some of the RF imaging coils, imaging software and devices being used in a scan are not approved by the FDA but are similar to counterparts that have been approved by the FDA. There is a small risk of heating from the cables associated with these devices.
The investigational devices used in scanning at the Lucas Center and CNI, including EEG/Physio/Eye-tracker devices, pose a non-significant risk to subjects in line with the criteria for exception from an IDE, and routinely used by many other experimenters at Stanford. There have been no serious adverse events incurred during scanning at the Lucas Center or CNI.

Brainsight™

Brainsight™ is a stereotactic image guidance system that facilitates the positioning of TMS coils over a subject's brain. It can display the stimulation targets (derived from MRI / fMRI images) on anatomical MR images, providing an interactive navigational guide for coil positioning. It has virtually no risks except for maybe minimal fatigue from holding the head still for a few minutes.

TMS

The TMS device to be used is the MagVenture X100 with MRI-compatible coil. The TMS devices are non-significant risk devices, in line with the criteria for exception from an IDE.
The principal components of the system are “figure-8’”style coil made of insulated copper bus bar and four capacitor-containing “booster modules”. The flow of electricity from the booster modules to the coil is regulated by a control module and a laptop computer. When a pulse of electricity flows through the coil, a magnetic field pulse is generated in accordance with Faraday’s law. This magnetic pulse, in turn causes nearby neurons to discharge in a physiological variant of the Hall Effect. No electric current is ever passed between the machine and the patient. Currently, this TMS machine has FDA approval for peripheral nerve stimulation only.

The TMS devices are also non-significant risk devices, in line with the criteria for exception from an IDE. Patients are generally able to drive home or return to work immediately after an rTMS session. The most common side effect of TMS (approx 25% of patients) is a mild headache, which usually responds to the over-the-counter medications such as ibuprofen. However, no difference in headache frequency between TMS and sham treatment was reported in the recent large trials (O'Reardon et al., 2007; George et al., 2010). The rTMS can cause some scalp pain at the application site, which is usually worse during the first few sessions and then largely disappears, although a few patients drop out of studies because of this discomfort (George and Post 2011). There is also a very small risk of toothache from TMS.

Studies suggest that the loud clicking noise produced by the TMS discharge may exceed 140 dB of sound pressure level, and can cause hearing loss (Rossi et al., 2009). A small subset of adults experienced transient increase in auditory thresholds post TMS. Permanent hearing loss was observed in a single individual who did not wear hearing protection. Although the majority of studies reported no change in hearing after TMS when hearing protection was used. A recent review showed no change in auditory threshold after 6-12 weeks of rTMS exposure (n=325) (Janicak et al., 2008). In our study, we require that all subjects and operators wear approved hearing protection (earplugs) during all TMS sessions as recommended by TMS safety guideline (Rossi et al., 2009).

Although rTMS are generally safe and well tolerated without enduring side effects, total 16 cases of accidental seizures induced with TMS were reported, with a sample size of several thousand patients and healthy volunteers exposed to TMS. The risk is estimated to be probably less than 0.5%. (George and Post 2011). The majority of cases reported were in healthy volunteers who received TMS to the motor cortex (the most epileptogenic region of the cortex) and the stimulation parameters were outside of the safety guideline now widely adopted (Wassermann 1998). Among the nine new cases reported after the publication of 1998 safety guideline, three of them (one case with TMS parameters outside safety guidelines) were considered to be likely non-epileptic, e.g. syncope, pseudoseizure with normal EEG; five of them (3 cases with TMS parameters outside safety guidelines) occurred in patients taking pro-epileptogenic medication (n=4) or following sleep-deprivation (n=1); one seizure case was associated with theta burst stimulation (TBS) (Rossi et al., 2009). Of note, TBS is not included in our study.

All of the seizures were self-limited, occurred during TMS administration when the subjects were sitting down and near an investigator, no medications or other interventions were required. Additionally, no recurrences were reported.

No enduring impairment of neurocognitive functioning in TMS patients has been reported. (George and Post, 2011).

Neuronetics, a TMS device manufacturer, sponsored one of the largest single studies of TMS (used for the treatment of depression) involving 155 active TMS subjects. There were no reports of any serious adverse events, including seizure (O'Reardon et al., 2007). A recent NIH sponsored, industry independent, randomized, active sham-controlled trail in depression found only minimal adverse effects reported by participants (n=190) that did not differ between active rTMS treatment group vs. sham (George et al, 2010).

In summary, TMS (single-pulse TMS and rTMS) are generally safe and well-tolerated, however, seizures remain a rare but significant adverse event. In our study, all stimulation parameters are determined to comply with the safety guidelines for TMS (Wasserman, 1998; Rossi et al., 2009). In the event of adverse effects related to MRI/fMRI scanning and TMS, safety coordinators and medical staff at the Lucas Center and CNI will be on-site for consultation and assistance. The Stanford University Hospital Emergency Room is less than a 5-minute walk from the Lucas Center or 10 minutes from CNI. Finally, Dr. Amit Etkin, the PI of this study, is a licensed physician and will oversee all research clinicians and monitor any adverse situations that might arise during the course of 20-40 sessions of rTMS at the psychiatry outpatient clinic, as well as the MRI/fMRI scans.

c. Use of Deception in the Study

Not applicable

d. Use of Audio and Video Recordings

Not applicable

e. Alternative Procedures or Courses of Treatment

The alternative to participation is not participation.

f. Will it be possible to continue the more (most) appropriate therapy for the participant(s) after the conclusion of the study?

This will not be possible. Daily rTMS treatment for MDD is intended to be a brief course of intervention. We do offer open-label rTMS to patients in sham group.

g. Study Endpoint(s)

The endpoint of the study is fMRI/TMS scans post rTMS treatment. Although this study involves rTMS and sham treatment, our goal is to explore the brain circuit involved in clinical improvement in response to focal, non-invasive brain stimulation with rTMS, not the efficacy of rTMS vs sham. In addition, we do offer open-label rTMS to the sham group.

Primary Outcome Measure:
Clinician administered HAM-D
The Hamilton Depression Rating Scale (HAM-D) is a 24-item clinician-administered assessment utilized as a way of determining a patient's level of depression before, during, and after treatment. It takes approximately 15-20 minutes to complete the interview and score the results.

Exploratory Outcome Measures:
fMRI/TMS assessed neural network connectivity [Time Frame: Up to 3 months.]
From pre- to post-treatment, improvement will be based on enhanced functional connectivity.

Implicit emotion regulation [Time Frame: Up to 3 months]

Implicit emotion regulation assessed through emotion conflict task performed during functional imaging. Performance based on reaction time and recruitment of emotion regulation regions during the task.

fMRI-assessed resting connectivity [Time Frame: Up to 3 months.]
From pre- to post-treatment of patients with high-frequency repetitive TMS (rTMS) improvement shall be measured by normalization of baseline network-level deficits.

3. BACKGROUND

a. Past Experimental and/or Clinical Findings

Depression is a highly prevalent and serious mental illness, has a lifetime prevalence of 16% (Kessler RC et al., 2003), and accounts for more global disability than any other illness (WHO, 2008). Studies such as STAR*D have illustrated the poor success rates of even the best-calibrated treatments. In fact, only 43% of STAR*D patients were able to achieve sustained recovery during the study period (Nelson, 2006). At the heart of this problem is the lack of a causal, mechanistic, neurobiological understanding of the pathophysiology of depression. Having such an understanding would allow the development of novel, neural network-targeting treatments.

We conducted resting-state functional connectivity (FC) analyses in a sample of 39 medication-free depressed subjects and 38 healthy controls, seeding the FC analyses with regularly-placed spheres throughout the entire PFC. We analyzed the groupwise difference at each of these seeds, measured as the number of suprathreshold voxels at $p<0.05$, the regions of greatest abnormality are in the ECN, and in particular its DLPFC node. As the patient sample analyzed here is reflective of the sample to be recruited for the proposed study, these data lend further support to targeting the pMFG with TMS/fMRI and conceptualization of network-level abnormalities in depression within the context of ECN-DMN interactions.

To test for causal and directional interactions between the ECN and DMN, we conducted concurrent TMS/fMRI in 11 healthy subjects, targeting the pMFG (ECN) and compared it to targeting a more anterior prefrontal region (aMFG), which is part of a cingulo-insular emotional salience network. Stimulation of the pMFG resulted, as predicted by correlational neuroimaging studies, in deactivation of regions within the DMN, most strikingly in the VMPFC. This effect was not seen after stimulation of the aMFG, where activation in the dorsal cingulate and insula was more evident, demonstrating site- and network-specific effects of stimulation. Interestingly, the individual functional connectivity-localized pMFG site was 5.1cm [SD 0.48] anterior to the primary motor cortex, thus consistent with localization using the "5cm rule," but now framed in the conceptual context of the ECN/DMN. These data demonstrate, for the first time, a causal, inhibitory relationship between the ECN and DMN, and makes possible a novel translation to depressed patients.

b. Findings from Past Animal Experiments

There is some animal work on the neural effects of TMS, though this has generally been limited to effects at the site of stimulation. These data show that TMS stimulation leads to coupled neural and hemodynamic changes at the site of stimulation that varies with stimulation parameters (Allen et al., 2007). These results support the use of blood flowmeasuring methodologies, such as fMRI, in detecting the neurophysiological effects of TMS stimulation in the human brain. No data, however, has been reported on use of TMS in the fMRI environment with animals.

4. DEVICES USED IN THE STUDY

a. Investigational Devices (Including Commercial Devices Used Off-Label)

Investigational Device 1	
Name:	RF Antenna Head Coil
Description:	Part of MRI head coil (custom)
Significant Risk? (Y/N)	No
Rationale for Non-Significant Risk	This device is a required accessory to the MRI machine that is involved in detecting the MRI signal in the brain. It is a custom-built version of a standard clinical coil
Investigational Device 2	
Name:	MagPro X-100
Description:	Magventure MagPro X100- TMS stimulator
Significant Risk? (Y/N)	No
Rationale for Non-Significant Risk	It is an FDA-approved for peripheral nervous system stimulation, not CNS use, however, there is an extensive experience of TMS devices being used inside and outside of the magnet, which confirms its NSR. No modification has been made to this device for our study.
Investigational Device 3	
Name:	TMS coil
Description:	Coil Cool-B65 A/P and Electrode Cable for Cool-B65
Significant Risk? (Y/N)	No
Rationale for Non-Significant Risk	These devices are required standard accessories to the TMS machine (MagPro X100) that are involved in generating magnetic pulses.
Investigational Device 4	
Name:	BrainsightTM
Description:	A stereotactic image guidance system facilitates the positioning of TMS coils over a subject's brain.
Significant Risk? (Y/N)	No
Rationale for Non-Significant Risk	A stereotactic image guidance system facilitates the positioning of TMS coils over a subject's brain. This procedure has virtually no risks except maybe minimal fatigue for subjects from holding the head still while wearing a swimming cap for a few minutes.
Investigational Device 5	
Name:	Sigma MR750 3T scanner
Description:	3.0 Tesla Magnetic Resonance Imaging device. Used to acquire functional and anatomical brain images.
Significant Risk? (Y/N)	No
Rationale for Non-Significant Risk	As specified

5. PARTICIPANT POPULATION

a. Planned Enrollment

40 subjects

b. Age, Gender, and Ethnic Background

Age Range: 18-50 years old
Gender: Males and Females
Ethnic Background: Any race or ethnic origin

c. Vulnerable Populations

Not applicable

d. Rationale for Exclusion of Certain Populations

We will include women and minorities. We will not include children as TMS work has primarily been done in adults, and therefore safety studies have not been comparably carried out in children.

e. Healthy Volunteers

No healthy volunteers are included in this study.

f. Recruitment Details

Participants will be recruited through advertisements in print and online media/websites such as craigslist.com, researchmatch.org, wesearchtogether.org, Stanford Report, and Google ads, placement of posters in public locations, targeting the entire San Francisco Bay Area. Participants will also be recruited through various clinics in Palo Alto, including Stanford Hospital and Clinics. We will provide fliers and a questionnaire at community events. In collaboration with other research teams, we will also collect interest cards from current research subjects who are interested in learning more about this study. Subjects will respond to the ads either by replying to the email posted in the ads or by calling the phone number listed. Subjects may also fill out the online interest card by visiting our website. Subjects can book their own appointments via checkappointments.com.

g. Eligibility Criteria [from CLINICAL TRIALS.GOV]

Inclusion Criteria:
Men and women, ages 18 to 50
Depression assessed through phone screen
Must comprehend English well to ensure adequate comprehension of the fMRI and TMS instructions, and of clinical scales
Has failed >1 previous adequate antidepressant medication trials
Right-handed
No current or history of neurological disorders
No seizure disorder or risk of seizures

Exclusion Criteria:
Any contraindication to being scanned in the 3T scanners at the Lucas Center or CNI such as having a pacemaker or implanted device that has not been cleared for scanning at the Lucas Center or CNI
Any unstable medical condition, any significant CNS neurological condition such as stroke, seizure, tumor, hemorrhage, multiple sclerosis, etc
Current rTMS treatment or prior treatment failure with rTMS
Current electroconvulsive therapy (ECT) or prior treatment failure with ECT
Currently pregnant or breastfeeding

h. Screening Procedures

Prospective participants will be known to meet as many of the inclusion/exclusion criteria as possible. Prospective participants will attend an in-clinic screening, where the project will be

explained and they will be invited to join the study by signing the informed consent. No one is considered to be a study participant until they attend the in-clinic screening and sign the consent form. After obtaining informed consent, screening will occur over a period not to exceed 3 weeks. Demographics and general medical history will be obtained including psychiatric history. A General physical and neurological exam will be performed including vital sign measurement, if applicable. A review of pre-study medications for up to 30 days prior to screening will occur. All eligible subjects will undergo structured diagnostic interviews, and clinical assessments. Although medication-free patients are ideal for our study due to minimal interference with TMS and fMRI, given the widespread use of antidepressants and benzodiazepines in this patient population, we are more likely to encounter patients who are already on antidepressants and/or benzodiazepines during screen phase, we will adjust, if clinically appropriate, some concomitant medications to make our recruitment less challenging, at the same time, without introducing significant confounding factor. Participants may be asked to complete a breathilizer and/or drug screen prior to sessions.

i. Participation in Multiple Protocols

We will ask the potential subjects if they are participating in any other protocols. They will be instructed not to participate in any other protocols during their involvement with our study without first getting prior authorization from both our research team and that of the other study. Overlapping participation will be handled on a case-by-case basis.

j. Payments to Participants

Participants will be offered $200 to complete the entire study.
-If found ineligible due to too high of a motor threshold prior to completion of Scan 2, participant will be paid for partial completion of the study in the amount of $75.
-Participants will be paid another $100 upon completion of the 6-month follow-up visit.
-If a participant is found to be eligible for the open-label portion of the study, he/she will be paid an additional $100 for completing that portion along with the accompanying assessment and TMS/fMRI scan.

No monetary payment will be offered for participation in TMS or sham treatment part of the study.

k. Costs to Participants

No costs to the subject will arise as a result of participation in this study, other than cost of their own transportation to and from the medical center, and the time involved.

l. Planned Duration of the Study

Five years

6. DATA SAFETY MONITORING PLAN (DSMC)

A project Data and Safety Monitoring Board (DSMB) will be set up by the Protocol Director, and will monitor the experiments detailed in this IRB proposal. The initial task of the DSMB will be to review the protocol, procedures manual and consent form to identify any necessary modifications. If modifications are necessary, revisions will be reviewed by the DSMB prior to its recommendation on initiation of the project. Throughout the study any changes to the protocol will be submitted to the DSMB. The DSMB, based on its review of the protocol, will identify the data parameters and format of the information to be regularly reported. The DSMB will be

informed of the occurrence of any serious adverse events and immediately notified of fatal or life-threatening events. The DSMB may at any time request additional information from the Project Director. Based on the review of safety data, the DSMB will make recommendations regarding the conduct of the study. These may include amending safety monitoring procedures, modifying the protocol or consent, terminating the study, or continuing the study as designed. The discussions and
decisions of the DSMB will be summarized in written reports and provided to the Project Director. The DSMB will meet in person or by conference call on a quarterly basis. The DSMB will also provide advice regarding any discrepancies found by the data auditing system or other sources.

7. BENEFITS

MDD patients will receive at no cost of rTMS, a new FDA approved, noninvasive treatment for MDD. Note that all subjects in this study will receive rTMS. The long-term benefit for society may be a more detailed understanding of MDD and mechanisms of change in rTMS, as well as the basis for development of a novel TMS treatment for MDD. All participants will be given pictures of their brain collected during fMRI sessions.

8. PRIVACY AND CONFIDENTIALITY

All participant information and specimens are handled in compliance with the Health Insurance Portability and Accountability Act (HIPAA) and privacy policies of Stanford University, Stanford Health Care, and Stanford Children's Health.

During screening, participants will meet in a private interview room with a member of the study team to sign the consent form, discuss the protocol, and determine suitability for enrollment. All interviews will be done in a private setting. Followup interactions will take place by private phone calls and emails to previously identified email addresses private to that participant. MRI and fMRI/TMS will take place in the MRI suite in the Lucas center, to which access is restricted except to study personnel. Similarly, rTMS treatments will be done in the TMS room in the Department of Psychiatry and Behavioral Science, to which access is restricted except to study personnel.

All data will be de-identified after acquisition. PHI and images or electronic data with PHI will be stored on physically secure and password protected computer servers behind a firewall.

Data and image files will be given a coded study ID number, and PHI removed from the raw data. The PI has the code key. Digital MRI images will be de-identified by Lucas Center staff at the time images are saved. MRI scans, from which facial information may be reconstructed (and thus an identifier) will be de-identified using conventional face stripping algorithms for MRI data.

9. CONSENT PROCEDURES

The persons obtaining consent will be one of the investigators, the study coordinator, or a research assistant, who have completed all required Stanford training in Human Subjects, Good Clinical Practice, and HIPPA, and have been trained to give informed consents. The consenting interview is always done after the potential research subject has been presented with a description

of the study and indicated interest in participating, and before any information is collected, or any questionnaires answered. The consenting interview typically takes place in one of the private interview rooms in the Department of Psychiatry. Enough time will be allowed in the consent discussion for the potential participant to make an informed decision, and to ask any and all questions they may have and discuss the study with the researchers. We estimate this will take between 30 minutes and one hour. The potential participant may take the consent home to discuss with family or others, and return later to sign it if they so desire. Every attempt will be made to ensure the participant does not feel coerced. We believe that the payment offered for participation is not great enough to entice a person to participate if they do not otherwise want to do so. Coercion and undue influence will be minimized by declaring all conflicts of interest should they exist, openly answering and soliciting any questions the subject may have and pointing them to online resources about TMS or fMRI if they want to read additional information about the techniques.

10. STATISTICAL ANALYSIS PLAN

For the depression group, t-tests and ANOVAs will be performed to examine the effect of rTMS treatment, compared to sham, on network activity by comparing the follow-up TMS/fMRI scan to the initial scan between those two groups (N=20/group) – doing so will determine the network changes associated with real rTMS, since we have a convincing sham control arm. Additionally, we will use multiple regressions to examine the relationship between network-level activity change and clinical response to rTMS treatment in the real treatment group. Baseline TMS/fMRI moderators of treatment response will be examined using multiple regressions in the real treatment group.

Power calculation: Not Applicable.