Title: The Effects of Repetitive Transcranial Magnetic Stimulation Prefrontal Target Location on Outcomes for Major Depressive Disorder

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Study Procedure Timeline and Protocol

Eligible patients will be identified during clinical transcranial magnetic stimulation intakes, which occur weekly in the psychiatry clinic (2JPP clinic). Interviews are conducted by physicians who are members of the research team. If a patient is identified as eligible for the study, he or she will be asked if they are interested in participating in the research study. If they answer yes, a study physician will set aside time at the end of the appointment to discuss the details, or will obtain information and permission to contact the patient over the phone after the appointment to provide details.

After detailed description of the study, if patient is willing to participate and meets study criteria, consent form will be signed. This will occur on the day the patient presents for initial testing as part of the research study. Once expressing interest, the patient will work with the study physician or a research team member to set up a date and time for the patient to come in for cognitive, psychological, and neurobehavioral testing, and, in a subset of patients, an MRI scan. If they choose not to participate, they will proceed with rTMS treatments as is standard clinical care.

Participants who are interested in the study will present for their baseline testing prior to initiation of their rTMS treatment course. The testing will occur in a designated research space, likely W264 or T212 in General Hospital. This is estimated to take 1-3 hours, depending on whether or not an MRI is included. These assessments include NIH Toolbox cognitive and emotional batteries (30-45 minutes), Temperament and Character Inventory (30 minutes), MOCA, CGI, PHQ-9 and MADRS (20-30 minutes total), and neurobehavioral testing and neurologic exam (30-60 minutes). Patients will have heart rate variability and facial movements monitored while viewing video clips or images, or hearing stories that may be emotionally charged or neutral (10-15 minutes). EEG will be recorded at rest and during tasks (30 minutes). Some patients may be given an actigraphy wristband to monitor their daily level of activity and their circadian rhythms. Some of these assessments are already obtained as part of the initial work-up for rTMS patients and that data is available for review under a separate previously approved IRB. The neuroimaging will include 21 minutes of resting state fMRI, T1rho, T1 MPRAGE, and DTI (<=60 minutes total). A research team member will escort the patients receiving MRIs to the MRI scanner and back. If a subject chooses to participate in the Vocal Pattern detection portion of the study, they will complete the procedures once weekly for the entirety of their TMS treatment course. The research team member will schedule this with the subject in advance so they are prepared for the length of the visit. Subjects will complete the PHQ9 questionnaire, if they have not already. Next, the recording part will begin with the reading the Grandfather Passage, and the Rainbow Passage. Finally, the subject will be asked some questions about your daily life and your interests.

The course of TMS will occur as clinically determined by the TMS physicians providing the patient's care. The only unique aspect is that patients in the study will be randomized to either receive rTMS at the F3 location (determined using free software from clinicalresearcher.org) or the 5.5cm method, as is the current standard of clinical care at the University of Iowa for clinical rTMS treatments. Some early internal data has shown that these targets can vary anywhere from a few millimeters apart to a few centimeters, but all targets are within the prefrontal cortex on the left side and consistent with the FDA-approved treatment region for major depressive disorder. The nature of these targeting strategies

should prevent any target from ever falling outside a clinically approved range, but if for some reason it appears that a target is outside of the FDA-approved target region, a study physician will be called to evaluate and confirm the targeting, and adjust if felt to be clinically inappropriate (e.g., not in the prefrontal cortex for that patient). Noninvasive autonomic measures will be obtained during the course of treatment including blood pressure, heart rate, pupil size, and facial movements, although this should not interfere with or delay the administration of the TMS therapy. Some of these measures are already intermittently obtained on patients undergoing TMS therapy.

Treatment will then proceed as managed by the clinical rTMS service at University of Iowa. Follow-up appointments will occur as clinically scheduled by the rTMS clinical service and the patient's other providers as is standard of care. The patient and raters will be blinded to the treatment target for each patient, which will be assigned randomly. The treatment technician will be aware of the treatment site as needed for performing the appropriate measurements and targeting procedure during appointments.

After a patient has either completed their rTMS course or the course has been terminated by the rTMS team for whatever reason, the patient will have the same testing performed as was performed at their initial study visit. This may include an MRI if patient consented to this and a pre-treatment MRI was conducted on the patient. For purposes of the study, the follow-up MRI could occur either at the very end of the treatment course or at some point during the treatment course, as determined by the study physicians and with patient approval/agreement. They will then be asked to schedule a follow-up phone call 4-6 weeks after completion of the rTMS treatment course, and some questionnaires may be administered over the phone at that time, including a PHQ-9. After this visit, they will no longer be a part of the study.

Recruitment

Patients will be recruited as described above. Only patients who come for and complete a clinical rTMS intake will be asked to participate in the study.

Determination of Treatment-Resistant Depression

Treatment resistant depression will be identified based on clinical interview by a physician with special training in rTMS or psychiatry. This will be a standard clinical interview that will confirm the diagnosis of major depressive disorder, rule out other causes of depression, and evaluate for previous failure of medication and psychotherapy trials. This is standard of care for rTMS treatment as determination of whether it is indicated for use for major depressive disorder, and thus occurs as part of every rTMS evaluation. After this appointment, further questioning may occur by the research study team if needed to confirm that patient meets study criteria or to clarify any information obtained during the clinical interview.

Inclusion Criteria

As per the IRB:

Inclusion:
-Diagnosis of major depressive disorder
-Age greater than or equal to 18 years
-Able to consent for treatment and research participation
-English-speaking
-Have been evaluated by a psychiatrist or neurologist with expertise in TMS and felt to be an appropriate candidate to undergo TMS treatments

Exclusion Criteria

As per the IRB:

Exclusion:
-Age less than 18 years
-Patients that are excluded during TMS assessment including:
-Patients with epilepsy or seizure disorder
-Patients with implanted ferromagnetic equipment in their face or skull near the stimulation target

MRI Exclusion criteria:
-Implanted device including pacemaker, coronary stent, defibrillator, or neurostimulation device that is not MRI-compatible
-Metal in body including bullets, shrapnel, metal slivers
-Claustrophobia
-Uncontrolled high blood pressure
-History of atrial fibrillation
-History of significant heart disease
-Hemodynamic instability
-History of kidney disease
-Pregnant

MRI

The MRI scan will occur as described in the study protocol. Only a small subset of all patients enrolled in the study will receive an MRI scan before and after the treatment course. These scans will be scheduled to coincide with the other parts of the study evaluation if possible. Patients who are asked to participate in the MRI portion of the study can choose to refuse to participate in the MRI portion and still participate in the other portions of the study, or can refuse all portions and receive rTMS as is the clinical standard of care. In a small subset of patients (n=25 approximately), a repeat neuroimaging or neurobehavioral assessment session may be completed partway through the TMS course to look for biomarker or imaging changes during the course of TMS. This will be arranged with the patient several days ahead of time with their consent, and they will have the option to decline to participate. If subjects take part in this MRI midway through treatment subjects will undergo a single session of TMS in a research area in close proximity to the research MRI scanners. We will be using the same protocol and parameters as the patients' clinically determined TMS sessions, and the same device (albeit a replica device purchased for research purposes). The purpose of this MRI and single session occurring in close

proximity to the scanners will be to allow for rapid post-treatment MRI to detect short-term function and metabolic brain changes.

Scales/Testing

All of the scales and testing involved in the study are as described above. The neurobehavioral testing that is discussed above is composed primarily of neuropsychological testing and emotional scales, as well as a neurologic exam (some portions of this, again, are already conducted as part of the standard work-up for the rTMS clinical service).

Targeting

Targeting either the F3 left prefrontal cortex location or the 5.5cm target location will occur as described above. Targeting the F3 location requires taking measurements of the head circumference, tragus-to-tragus distance, and nasion-to-inion distance, and using computer software to calculate the correct prefrontal target using head landmarks. The 5.5cm target location is determined by measuring 5.5cm anterior to the primary motor cortex of the brain, which is identified using a TMS procedure called motor threshold testing, all of which is done as part of the standard of care in clinical rTMS and will not be altered for this study. Targets will be marked onto a swim cap which the patient will wear during treatments, to ensure that the same target can be stimulated from treatment-to-treatment reliably, again, as is standard practice in rTMS treatments.

Treatment as Usual (Parameters)

Treatment parameters other than stimulation location will be as per clinical standard of care, including 3000 total pulses at a frequency of 10Hz, with 4-second train duration, 26-second off time, for 75 total trains. All treatments will be targeted at the left prefrontal cortex as is FDA-approved for major depressive disorder, and all treatment targets will fall within this region.

Safety

All treatments will follow the standard of care safety procedures for clinical rTMS. An rTMS-trained technician will be present with each patient during the entirety of their treatment, with a study physician immediately available if needed for emergent response (such as for induced seizure). There is no evidence to suggest the risk of seizure is higher with stimulation at either target being investigated in this study. Management of seizure will occur as is standard practice for clinical rTMS. If a patient were to indicate suicidal thoughts during the course of their work-up and evaluation for this study, it would be managed as per standard of care for the clinical rTMS service, which involves a thorough safety risk assessment by a team physician, appropriate safety planning, and transfer to a higher level of care as clinically indicated. This may involve anything from providing additional resources for crisis intervention, discussion with the patient's primary psychiatrist or family (if patient provides consent to do so), or transfer to an emergency room for further evaluation. As a study physician will be either conducting all portions of the study evaluation or immediately available, and all study physicians

involved are also involved in standard clinical rTMS care, this should not be onerous and should be well within the scope of the team's clinical abilities.