**PROTOCOL TITLE:**

**Randomized controlled trial of EEG/fMRI Controlled TMS For Treating Depression**

**PRINCIPAL INVESTIGATOR (for the R33 IRB application):**

- Mark S. George, MD
- Truman Brown is the PI for the R21 phase, and is the named PI on the combined two stage grant. EEG-TMS-fMRI (Pro00042072)

## 1.0 Objectives / Specific Aims

We have completed the first R21 phase of this combined two phase grant. Please see the attached progress report to the NIMH for a full update on what we have done to date. Essentially, we succeeded in creating for the first time on planet Earth a fully working combined and integrated TMS-fMRI-EEG system, and then used that in healthy controls to show that the secondary effect of the TMS pulse is greater when it is delivered to the cortex during the rising phase of the EEG alpha wave for that person. We then also showed that we can monitor a subject with EEG and then predict and time a TMS pulse to be able to hit this time window. This work was covered under the MUSC IRB EEG-TMS-fMRI(Pro00042072).

The goal of the R33 phase of this R21/R33 grant is to test the hypothesis that synchronized stimulation has clinical implications; specifically, that the increased ACC inhibition due to increased cortical activation of the DLPFC by synchronizing the TMS pulse application to an individual patient's alpha rhythm will have a significant effect on the anti-depressive treatment response rate for TMS, sufficient to justify a future, more extensive clinical trial.

As the R33 phase is a stand-alone clinical trial, we will submit a separate IRB application.

In this study, we will look first at the BOLD activity from the ACC as a measure of target engagement because there is a substantial literature suggesting that reductions in activity in the ACC are an integral part of the depression network and may predict eventual antidepressant effect. [1-5] Moreover, we and others have shown that stimulation of the left DLPFC causes a reciprocal change in ACC. [6-9]. The studies proposed for the R33 will randomize a cohort of 60 medication free depressed patients to standard TMS treatment (NON-SYNC) or timing optimized TMS treatment (SYNC). For the later cohort we will use the results of the R21 phase to measure the optimum timing of the TMS pulses with respect to each individual's EEG rhythms to maximize inhibition of the ACC following TMS. This will be done at entry into the trial and after the therapy is complete. Both experimental and control group will undergo these measurements but they will only be used in the former group. To enable the 4 week (5 days/wk) TMS treatment plan to be able to use this individually determined timing, we will integrate a second EEG system with our treatment TMS unit. Our R33 specific aims are:

**Specific Aim 1:** *Integrate a similar EEG system with our treatment TMS system with similar feedback circuitry as that in SA 3 in the R21.*

**Specific Aim 2:** *Carry out a 4-week trial (2 extra weeks for responders but not remitters) of anti-depressive therapy randomized between optimum timed TMS (SYNC) and standardized non-synchronous TMS (NON-SYNC) in a cohort of depressed patients to estimate the success rate of such an optimized treatment.*

This study will provide the data needed for a go/no-go decision on a full clinical trial for this potential novel therapy.

Hypothesis: In a double blind, randomized (1:1) trial enrolling only at MUSC over three years in 60 treatment resistant depressed patients, we hypothesize that daily prefrontal rTMS over 4-6 weeks with the initial TMS pulse of each train synchronized to the subject's alpha phase (SYNC TMS), will result in improvement in depression, and that these improvements will be greater than the improvements seen using the same form of treatment but not with the initial pulse synchronized (NON-SYNC). As this work is a first ever use of this technology, we wish to compare the antidepressant effects to standard therapy to see if synchronization boosts the clinical effect. We have done a power analysis for this number of subjects but we are really most interested in comparing the overall outcome between the two groups, and looking at response predictors. Thus it is not a formal efficacy or even inferiority trial, rather a comparative early phase trial.

## 2.0 Background

Daily prefrontal TMS for depression, as developed by the PI, involves delivering TMS pulses to the prefrontal cortex and not assessing what the actual EEG phase is of the person's brain. In cardiology, in order to stimulate the heart effectively, one has to know the rhythm and phase of the heartbeat in order to perform cardioversion. We wonder if it is important to time the brain stimulation with the phase of the person's brain. We know that the brain has definite rhythms, and cycles through being excited or resting. A common EEG rhythm is alpha frequency. Theoretically, the effect of the TMS pulse might be diminished if it was delivered when the brain was temporarily cycling into an off state.

In the r21 part of this grant, we designed and constructed a combined TMS/EEG/fMRI system. With that equipment we have shown that TMS pulses have different effects deeper in the brain as a function of the EEG alpha phase. Pulses delivered during an individual's optimized phase produce larger blood flow changes deeper in the brain than do pulses delivered during a falling phase.

In the R33 phase of the grant we now take that idea into a small clinical trial in depression to test if synchronized pulses have a larger clinical effect than do non-synchronized pulses.

## 3.0 Intervention to be studied (if applicable)

The SYNC and NON-SYNC treatment groups will receive the following dose of rTMS delivered over the left prefrontal cortex**: 6-13 Hz, 120% Motor Threshold*, 40 pulses per train, 3-7 second pulse train, 6-14 second intertrain (IT) interval **, 3000 pulses per session, one session per weekday**. This will initially be delivered for a fixed 4-week interval. For those individuals showing clinical response, they will continue getting their initial treatment (SYNC or NON-SYNC) up to 6 weeks total. [*Although the treatment will be administered at 120% of Motor Threshold, the treatment course will have a ramp up period with the first treatment at 100% of Motor Threshold and the second treatment at 110% Motor Threshold] **Interruptions** - Every attempt shall be made to complete each treatment session as per the protocol. Interruptions during the treatment are allowed as needed for patient comfort or convenience by using the "pause" selection on the device. However, an incomplete treatment is will be recorded. In the event that a treatment is missed: 1 or 2 days missed, continue into the subsequent week to complete the missed days. Evaluation should still occur after every 5 treatments. 3 or more days in a row – treatment must be aborted and the subject discontinued from their current phase and likely dropped from the study. **Evaluation After Every 5 Treatment Sessions and at the end of the 4$^{th}$ week** - At the end of each week of treatment, or after every five treatment sessions, patients will have the following assessments performed by a qualified individual who is masked to the subject's assigned treatment group: Hamilton Depression Score (Ham-D 28 item, Inventory of Depressive Symptomatology Self-Report (IDS-SR), Montgomery-Asberg Depression Rating Scale (MADRS), Global Assessment of Functioning (GAF), Clinical Global Impression (CGI).

## 4.0 Study Endpoints (if applicable)

Remission, as defined by HRSD24 <10.

Safety will be assessed by using information on all relevant adverse events experienced, as well as pre- and post- primary treatment testing of cognitive functions and fMRI studies to determine target engagement.

## 5.0 Inclusion and Exclusion Criteria/ Study Population

*Patients will be referred from other psychiatrists or may self-refer after hearing about the trial from email broadcasts, or mailings to psychiatrists. At least during the first year we will not formally advertise.*

**Rationale for Subject Selection Procedures**. A summary of inclusion/exclusion criteria for Phase 1 study entry are presented in Table E.1.

A brief note about this clinical trial and R-DOC criteria. While we embrace the notion of RDOC, and have listed a continuum of behavior (emotion regulation) and a well-defined target (ACC inhibition), we need to compare whether this new form of TMS improves on the current state of the art. All prior TMS studies in depression have used DSM-IV criteria for inclusion and exclusion. Thus, in order to reasonably compare this trial to those done in the past, we will resort to DSM-IV criteria for inclusion and exclusion criteria, while still examining the continuum of behavior and assess target engagement.

***Table E.1 Inclusion and Exclusion Criteria for Study Entry***

| | |
|---|---|
| 1. Diagnosis of unipolar major depressive disorder, in a current major depressive episode, without psychotic features | SCID-P to derive DSM-IV criteria |
| 2. Pretreatment Hamilton score ≥ 20 | Hamilton Rating Scale for Depression [24-item] |
| 3. Age between 21 and 70 years | Self-report |
| 4. Fixed and stable antidepressant medications for 3 weeks prior and during the rTMS trial. Limit on benzodiazepines to lorazepam (or equivalent) up to 3 mg every day | Physician evaluation |
| 5. Moderate level of resistance to antidepressant treatment in the current episode, defined as failure of 1-4 adequate medication trials or intolerance to at least 3 trials, and duration of current episode ≤ 3 years | Antidepressant Treatment History Form (ATHF) and physician evaluation |
| 6. No primary diagnosis of schizophrenia, schizoaffective disorder, other [non mood disorder] psychosis, depression secondary to a medical condition, mental retardation, substance dependence or abuse within the past year (except nicotine), bipolar disorder, psychotic features in this or previous episodes, amnestic disorder, dementia or MMSE ≤24, delirium, obsessive compulsive disorder, post-traumatic stress disorder, panic disorder | Physician evaluation, Mini Mental Status Exam (MMSE) |
| 7. No current Vagus Nerve Stimulation | Medical history |
| 8. No history of failing to respond to an adequate course of ECT in this or any episode, and no ECT within the past 3 months | ATHF and physician evaluation |
| 9. No contraindication to MRI | Physician evaluation; medical history |
| 10. No contraindication to rTMS (history of neurological disorder or seizure (except induced by ECT), increased intracranial pressure, brain surgery, or head trauma with loss of consciousness for >15 minutes, implanted electronic device, metal in the head, or pregnancy) | Physician evaluation; medical history; MRI; urine pregnancy test |
| 11. No unstable autoimmune, endocrine, viral, or vascular disorder. No unstable cardiac disease, uncontrolled hypertension, or sleep apnea | Physician evaluation; medical history |
| 12. No active suicidal intent or plan, or history of attempt within the past 12 months | Physician evaluation |
| 13. Willing to provide informed consent | |

Patients with unipolar major depression meeting the above criteria will be enrolled. The baseline HRSD score (24-item) must be >20. To ensure that baseline levels of depression severity are stable at the time of study enrollment, patients will be dropped if they show > 30% improvement in the HRSD score from the time of initial intake (e.g., screening) to the baseline assessment.

All subjects will have an MRI scan after obtaining consent but before being randomized.

Measures to increase sample homogeneity employed in this study include ruling out comorbid psychiatric and neurological disorders and selecting for a moderate level of medication resistance. These measures were considered to be the most likely context to provide a test of the antidepressant value of rTMS under ideal, controlled conditions, where we can fully assess whether synchronization matters. If synchronized rTMS is shown to have greater efficacy in this controlled setting, future work on the effectiveness of SYNC rTMS could be conducted in a more heterogeneous sample. To increase the likelihood of antidepressant response in the current study, Axis I disorders other than unipolar major depression will be excluded. While comorbid Axis II disorders are likely to be a predictor of worse antidepressant response, it is also acknowledged that Axis II disorders are difficult to diagnose accurately with a cross-sectional assessment during an acute major depressive episode. Furthermore, comorbidity of Axis II disorders and depression is frequently seen (especially in medication resistant samples) and can be expected to represent a sizable proportion of potential subjects for this study. Therefore, we will not exclude patients on the basis of Axis-II disorders, but we will use the MINI to collect information to characterize the sample, and to provide data on the impact of Axis II on therapeutic response with rTMS.

Medication resistance is a significant predictor of response to antidepressant medications and ECT.[10-15] Therefore, the level of medication resistance will be carefully measured in this study using the Antidepressant Treatment History Form (ATHF), which has been validated in large multi-center trials of ECT and VNS. To provide a fair test of the antidepressant value of rTMS, we will limit the degree of medication resistance to no more than 4 adequate trials in the current episode because it is expected that these patients will be less likely to respond to any treatment. Likewise, patients with chronic depression who have been in the current episode for longer than 3 years, or who have failed an adequate trial of ECT [11], will be excluded. At the same time, we do not want to falsely inflate the overall placebo response rate and jeopardize our ability to distinguish SYNC from Non-SYNC rTMS by including patients who have no degree of medication resistance. Most prior work with rTMS showing evidence of efficacy of active rTMS relative to sham included medication resistant patients. Thus, to minimize the overall sham response rate, we will only enroll patients who have failed at least one antidepressant trial or are intolerant to 3 medications. The reason for that failure to respond may be due to medication resistance (in the case of an adequate trial) or may be due to medication intolerance (resulting in an inadequate trial). While treatment intolerance and treatment resistance represent separate phenomena, both groups of patients are candidates for rTMS. Furthermore, failure to respond to a medication trial, regardless of its adequacy, may provide some rough indication of the likelihood of a placebo response.

An additional aspect of depression severity and chronicity that will be carefully considered in this protocol is that of suicide risk. The outpatient setting, and the possibility of receiving up to 6 weeks of SYNC rTMS stimulation (if it were to be less effective than current state of the art), represent a clinical context in which the risk of suicide needs to be carefully considered. For these reasons, patients with current active suicidal intent or plan, prior attempt within the last 6 months, or who in the judgment of the investigator would be at elevated risk for suicide will be excluded.

Because prior work has suggested that response to rTMS is suboptimal in depressed patients with psychotic subtype, patients with any history of psychotic features will be excluded. Another suggested predictor of response with rTMS is age. While prior work has suggested that the efficacy of rTMS may be lower in the elderly[16, 17], this is now thought to relate to the presence of cortical atrophy, resulting in an under-dosage of rTMS. We will include patients up to the age of 70, which will permit us to assess the utility of this dosage adjustment method.

Unlike some prior work with rTMS, this study will test the efficacy of rTMS with patients on fixed but stable concurrent psychotropic medications. This will eliminate the need for all patients to undergo medication washout prior to rTMS, and will greatly facilitate recruitment. Patients who have taken benzodiazepines chronically may not be able to tolerate dosage reduction to no more than 3 mg of lorazepam, and additionally may be at risk for withdrawal associated lowering of seizure threshold. Such patients will therefore be excluded. Another aspect of the patient's current depression treatment program may include psychotherapy. With the intention to study the stand-alone efficacy of SYNC or NON-SYNC rTMS in the absence of other treatment regimens, we will limit the frequency of visits with

the referring psychiatrist and/or therapy to no more than once per month. Additionally, no new psychotherapeutic relationships will be initiated during the study.

Patients with comorbid neurological disorders will be excluded as these may affect response rate, and may represent a contraindication to rTMS. Conditions increasing risk of seizure (e.g., history of seizure, head trauma, increased intracranial pressure, or space occupying brain lesion) will be excluded because seizure is a known risk of rTMS. Pregnant women will be excluded because of the unknown risks of the magnetic stimulation on the fetus. In the future, if rTMS becomes a proven treatment for major depression, its safety in the context of pregnancy should be studied[18].

A final consideration for enrollment will be the clinical appropriateness of study enrollment, both in terms of patient safety and their ability to comply with the treatment protocol. Patients judged not likely to be able to comply with the intensive daily rTMS treatment and follow-up visits will be excluded in order to minimize drop-outs and provide an adequate sample size for the continuation phase data to be meaningful.

Patients meeting inclusion/exclusion criteria will be offered participation, regardless of gender or racial/ethnic group. The sample composition will reflect the distribution of patients with MDE at each of the participating sites. Although the epidemiology of depressed patients who have failed medication trials has not been systematically assessed, women have a higher prevalence of major depression than men and might be somewhat overrepresented in our sample (60% women).

Inclusion and Exclusion for Healthy Control Comparison Group.

| | |
|---|---|
| 1. No Current or Past History of unipolar major depressive disorder, in a current major depressive episode, without psychotic features | *MINI to exclude DSMV criteria* |
| 2. Pretreatment Hamilton score < 5 | *Hamilton Rating Scale for Depression [24-item]* |
| 3. Age between 21 and 70 years | *Self-report* |
| 4. Not taking antidepressant medication | *Physician evaluation* |
| 5. No history of schizophrenia, schizoaffective disorder, other [non mood disorder] psychosis, depression secondary to a medical condition, mental retardation, substance dependence or abuse within the past year (except nicotine), bipolar disorder, psychotic features in this or previous episodes, amnestic disorder, dementia or MMSE ≤24, delirium, obsessive compulsive disorder, post-traumatic stress disorder, panic disorder | *Physician evaluation, Mini Mental Status Exam (MMSE)* |
| 6. No current Vagus Nerve Stimulation | *Medical history* |
| 7. No history of failing to respond to an adequate course of ECT in this or any episode, and no ECT within the past 3 months | *ATHF and physician evaluation* |

| | |
|---|---|
| 8. No contraindication to MRI | *Physician evaluation; medical history* |
| 9. No contraindication to rTMS (history of neurological disorder or seizure (except induced by ECT), increased intracranial pressure, brain surgery, or head trauma with loss of consciousness for >15 minutes, implanted electronic device, metal in the head, or pregnancy) | *Physician evaluation; medical history; MRI; urine pregnancy test* |
| 10. No history of autoimmune, endocrine, viral, or vascular disorder. No unstable cardiac disease, uncontrolled hypertension, or sleep apnea | *Physician evaluation; medical history* |
| 11. No active suicidal intent or plan, or history of attempt within the past 12 months | *Physician evaluation* |
| 12. Willing to provide informed consent | |
| | |

We will recruit these subjects from patient referral, MUSC broadcast emails, advertisement flyers, and word of mouth.

## 6.0 Number of Subjects

We plan to consent up to 100 depression subjects in order to randomize 60 patients to treatment in the clinical trial. Some patients will drop out between consent and randomization.

We also plan to consent and MRI scan 30 non-depressed healthy adults for comparison of the fMRI results. These control subjects will also receive one session of TMS as a treatment and will have two TMS-EEG-fMRI sessions. They are thus different than the healthy controls covered under the companion IRB application started with the R21. *EEG-TMS-fMRI ( Pro00042072 )*

## 7.0 Setting

Subjects will be screened and rated in Brain Stimulation Offices on the 5th floor of the IOP, or in screening rooms at the 30 Bee St. MRI facility, or electronically via Doxy.me. The MRI imaging will be done on the 3 Tesla research MRI scanner at 30 Bee Street. The TMS treatment will be done on the 5th floor of the IOP in Brain Stimulation Laboratories.

### *Study Sites*

MUSC is the only enrolling site for this clinical trial.

## 8.0 Recruitment Methods

Potential Depressed Subjects will be recruited largely by word of mouth and by alerting all MUSC psychiatrists about this free clinical trial. Currently there are many patients who meet this

study's entrance criteria but who do not have insurance, or whose insurance company denies coverage, or who have very large copays. This trial offers the standard FDA approved TMS as one arm, and the slightly modified SYNC form as the other arm. It is improbable that the SYNC will make TMS less effective. Thus this will be seen in the community as an opportunity to get free TMS. MUSC BSL doctors perform 2-3 consults per week regarding brain stimulation treatments for depression and we will remind these physicians about this trial. We will also post advertisement flyers around the MUSC campus and on MUSC online message boards. A third party online advertisement campaign will also be used.

Potential Subjects will be referred largely from the BSL consults, although we will also accept patients who hear about the trial and contact us directly. We will require that all subjects have a treating psychiatrist who will manage their care after the trial.

## 9.0 Consent Process

Only Dr. George or another member of the BSL physician group can obtain consent for patients. Research assistants may obtain consent for the healthy control subjects. Subjects will be given a copy of the current consent and HIPAA and encouraged to read over before attending official informed consent visit with well-educated study staff. Depressed subjects will also be encouraged to discuss with their current doctor on whether study might be appropriate for them.

The MUSC BSL has been conducting clinical trials with rTMS in depression for over 15 years now. We thus have a large network of psychiatrists and other providers who have referred depressed patients for rTMS treatment. Additionally, since 2008 we have also been delivering clinical rTMS for treating depression. Within the past year, SC now has Medicare and blue cross blue shield coverage for rTMS. Unfortunately, the insurance providers have set very high requirements for reimbursement (failure of >3 treatments in the current episode, documented failure of a course of CBT), and they also have high copays for treatment. We thus have a situation, and will likely continue to have, where there is high local demand for rTMS but an inability to deliver the care due to cost, and partial reimbursement. This trial is designed to be successful in the Charleston region as patients will be able to get FDA approved treatment, or a slightly modified version that is likely even better, for free. We think this economic incentive will greatly help with recruitment. With a $100- $200 copay or cash cost for each session, a course of rTMS (5/week for 6 weeks) costs each patient $3000-$6000. We will additionally reimburse patients for their travel and will provide compensation for MRI scans. This economic incentive has greatly helped in past treatment trials at MUSC.

We have conducted over 15 different rTMS treatment studies at MUSC and we have routinely met or exceeded our projected recruitment goals. We typically recruit by contacting MUSC psychiatrists and staff, have an informational session with local psychiatrists along with targeted mailings and phone calls, and then have broadcast emails to MUSC employees. We have also periodically employed Google ads. Television and print ads have not historically been successful. We have had over 90% retention in all prior rTMS depression studies, in part because we prioritize good communication with subjects and work very hard to make sure that their visits are on time and we are not late.

When the clinical trial begins we will have weekly staff meetings and monthly recruitment tracking, collaborating with NIMH staff if they would like. The DSMB will be notified yearly of recruitment process and every 3 months if study enrollment is < 50% of projected. We will work hard to inform subjects of the need to return for the 3- and 6-month follow-up visits.

Subjects will be given a copy of consent and HIPAA prior to coming in for official consent visit so as to read documents. Educated and qualified staff will go over in a detailed manner the current consent form and answer any questions the potential subject may have. If potential subject is still interested in starting the study both staff and subject will sign and date informed consent document. A signed copy of the informed consent document will be given to the subject.

This will be done in the MUSC BSL research offices on the 5th floor of the IOP or electronically via Doxy.me.

There will be no imposed time between informing the subject and obtaining consent. Subjects will be given a copy of the current consent and HIPAA and encouraged to read over before attending official informed consent visit with well-educated study staff. Subjects will also be encouraged to discuss with their current doctor on whether study might be appropriate for them.

In the consent forms and discussions with an investigator, patients are advised fully of the procedures to be used, the amount of time required of them, the fact that this study involves random assignment to two forms of TMS, only one of which has been tried before, the nature of the study and follow-up, the research procedures that will be conducted, the possible risks and benefits of the procedures, their right to refuse participation in the study without prejudice, their right to terminate participation at any moment without prejudice, and the name and telephone number of the Principal Investigator. All subjects will be required to have capacity to consent.

## 10.0 Study Design / Methods

This is a prospective randomized 4-6 weeks clinical trial with patients randomized 1:1 between SYNC and Non-SYNC TMS. Non-SYNC TMS is FDA approved and it is unlikely that SYNC TMS will be less effective than current practice. There is thus no sham or placebo control condition in this study, and all subjects are likely to benefit clinically. The MRI scanning session pre-TMS treatment will be split into 2 sessions. Visit 1 should take approximately 45 minutes with the whole time in the MRI scanner. Visit 2 should take approximately 180 minutes with 90 minutes in the MRI scanner. If the post-TMS treatment MRI is completed, the visit will last approximately 3 hours.

There is only one phase of this clinical trial.

All procedures are research only and there are no clinical procedures being performed.

The SYNC and NON-SYNC treatment groups will receive the following dose of rTMS delivered over the left prefrontal cortex: ***6-13* Hz, 120% Motor Threshold*, 40 pulses per train, *3-7* second pulse train, *6-14* second intertrain (IT) interval **, 3000 pulses per session, one session per weekday**.

This will initially be delivered for a fixed 4-week interval. For those individuals showing some degree of clinical response (defined as percentage change in HDRS score from baseline >25%), they will continue getting their initial treatment (SYNC or NON-SYNC) up to 6 weeks total. [*Although the treatment will be administered at 120% of Motor Threshold, the treatment course will have a ramp up period with the first treatment at 100% of Motor Threshold and the second treatment at 110% Motor Threshold]

We will differentiate the two groups solely on whether the TMS pulses are applied at an individual's phase optimum (individual alpha frequency (IAF) phase locked) or not. The two groups will both have rTMS applied at the individual's IAF (this is done because if the rTMS pulse train is at a different frequency it will no longer be at the correct phase after less than ¼ of the 4 second train) but in one group the initial TMS pulse will be phase-locked to the individual's optimum (as determined by a prior EEG/TMS/fMRI study using the instrument developed in the R21) and in the other group the TMS pulse will be applied at a random phase. The only difference between the two groups is the phase-locking of the pulse train. This active phase-locked condition is designed to maximize the target engagement we have demonstrated by increasing the response in the ACC so as to increase the likelihood of a stronger clinical antidepressant effect. By doing this we will be able to demonstrate whether applying rTMS at an optimum phase has a larger clinical effect on remission rates. If there are substantial clinical differences between the two groups, then we know that phase locking of rTMS to the optimum phase has a demonstrable antidepressant clinical effect.

**Interruptions** - Every attempt shall be made to complete each treatment session as per the protocol. Interruptions during the treatment are allowed as needed for patient comfort or convenience by using the "pause" selection on the device. However, an incomplete treatment will be recorded. In the event that a treatment is missed: 1 or 2 days missed, continue into the subsequent week to complete the missed days. Evaluation should still occur after every 5 treatments. 3 or more days in a row – treatment must be aborted and the subject discontinued from their current phase and likely dropped from the study.

**Evaluation After Every 5 Treatment Sessions and at the end of the 4th week.** The Inventory of Depression and Anxiety (IDAS) will be assessed at the baseline and at the end of treatment course. Brief COVID-19 questionnaires will be used to assess perceived threat, impact and experiences assessed at baseline, end of treatment and in follow-ups. At the end of each week of treatment, or after every five treatment sessions, patients will have the following assessments performed by a qualified individual who is masked to the subject's assigned treatment group:

Hamilton Depression Score (Ham-D 28 item),

Inventory of Depressive Symptomatology Self-Report (IDS-SR),

Montgomery-Asberg Depression Rating Scale (MADRS),

Global Assessment of Functioning (GAF),

Clinical Global Impression (CGI).

*(Upload in eIRB all surveys, scripts, etc.) Include what data will be collected.*

## 11.0 Specimen Collection and Banking (if applicable)

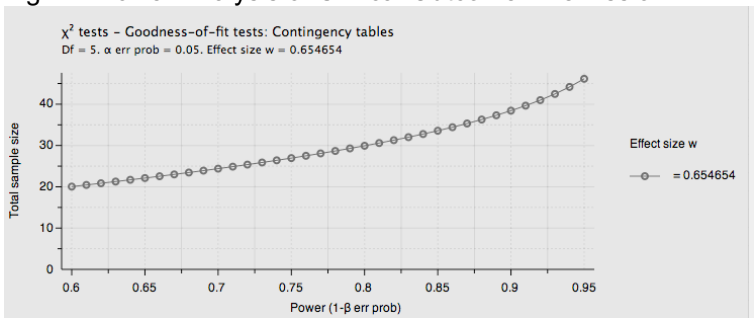
- The only specimens will be MRI scans before and after treatment, EEG data and rating forms.

## 12.0 Data Management

- *Describe the data analysis plan, including any statistical procedures.*

Remember that the R33 clinical trial is not meant to be a definitive trial of SYNC rTMS. Rather, it is designed to test whether synchronization of the TMS pulse with the subject's brain activity produces a markedly better response than the current approach to treatment, which is NON-SYNC. We thus reason that we need to see a clinically meaningful additional remission rate with SYNC versus NON-SYNC, in order for future definitive trials to be conducted. MRI scanning is expensive and having TMS machines that sync with the patient's EEG are more complex and expensive than the current methods. We thus are powered in this R33 to detect a very large effect size (0.65).

Fig 1D. Power Analysis of Clinical Outcome - Remission




The best trials of daily left prefrontal rTMS with focal figure eight coils are the industry sponsored Neuronetics trial, and the OPT-TMS trial. With inclusion and exclusion criteria very similar to the current trial, in the open label phases, they each achieved about a 30% remission rate. Published remission rates for ECT in a similar population in open label studies are roughly 60%. This current trial, although there is a randomization, are more like open label studies in that all subjects will be told they are getting some form of TMS. Fig 1D shows that consenting 60 subjects to get 50 completers has a .95 power of detecting this large of a difference, using a

simple chi-square comparison of remitters across the two groups. An additional aspect of the proposed clinical trial will be to provide researchers with the exact differences in remission, if there are any. Those can be integrated with future refinements and developments of rTMS. Thus, even if the effect size difference is not terribly large, one may wish to perform SYNC TMS in initial NON-SYNC responders. Moreover, we will examine the imaging and demographic variables to potentially identify response predictors that might guide future work.

The procedures to minimize bias in allocation of participants to treatment and in assessment of outcomes. After completion of the MRI scan, patients will be randomly allocated to either SYNC or NON-SYNC rTMS automatically by a computer program using a randomization table Once assigned, the person's number is in the trial database that exists on the computers that drive the TMS machines. Thus, each time the patient is treated, the computer will drive the TMS system at either the patient's SYNC phase, or NON-SYNC. No one who ever contacts the patient or touches the clinical data will know the randomization status, until all study subjects have completed the trial and the clinical trial dataset has been locked. The pre and post TMS/fMRI assessments of changes in ACC BOLD are analyzed in a machine driven fashion that is independent from researcher input or bias. The clinical ratings and assessments are performed by trained research nurses who are blinded to the subject's randomization. We will also ask patients, treaters and raters to guess whether they think patients are getting SYNC ed or NON-SYNCED treatment, and why. Any unblinding will be immediately reported to Drs. George and Brown, who will work to minimize spread of unblinding and will institute procedural changes to prevent a re-occurrence. These procedures have worked well in prior rTMS depression trials at MUSC. Describe the steps that will be taken to secure the data to maintain confidentiality (e.g. training, authorization of access, password protection, encryption, physical controls, certificates of confidentiality, and separation of identifiers and data) during storage, use, and transmission.

**Overview of data analytic plan** 1) Sample size: 60 patients, at a single MUSC site, will be randomized to SYNC or NON-SYNC TMS conditions. We expect that 90% (54 of 60) will be completers, and 80% (48 of 60) will be fully adherent. [See OPT-TMS manuscript for definitions of completer and fully adherent status.] These estimates are conservative and are based on our experience in conducting randomized, sham-controlled rTMS trials. Likely due to chronicity of illness and relative treatment resistance, most patients seeking rTMS are highly motivated, would not be considered "symptomatic volunteers" (for example, advertising for patients is not included in the budget). These factors have historically limited dropout and protocol violations.

2) Intent-to-treat, completer and fully adherent samples: The main analysis will focus on the intent-to-treat (ITT) sample. The ITT sample is defined as all randomized patients who receive at least 1 rTMS clinical treatment. Secondary analysis will be performed on two sub-samples: (a) completer sample and (b) fully adherent sample. The completer sample comprises patients who are evaluated after 4 weeks of treatment or terminate (and are evaluated) sooner based on investigator judgment that maximal clinical improvement had been obtained (regardless of remission status). In other words, completers are those patients in whom the maximal number of treatments was given or who terminate sooner due to the judgment that further treatment will not result in additional improvement (and who completed the 4 week fixed dose period). Patients who terminate the study early for any other reason [eg, withdrawal of consent, adverse event, etc.] do not contribute to the completer sample. Any patient who misses 3 consecutive scheduled rTMS sessions is withdrawn from the study. The fully adherent sample is a subgroup of the completer sample. This group comprises all patients who completed without a significant protocol violation. Significant protocol violations would include equipment malfunction or any reason a session is cancelled, reported and limited use of a prohibited pharmacological agent or illicit drug, etc. In addition, fully adherent patients can reschedule at most 2 sessions during the treatment phase.

3) Significance testing: All tests will be two-sided, performed at significance $\alpha$=0.05, except where noted.

4) Preliminary analysis: All variables will be examined for outliers at all time points using multivariate and univariate techniques before specific statistical models described below are applied in hypotheses testing of interest. The distributions of all continuous variables will be checked for normality, and transformations will be employed, if necessary, before applying specific parametric techniques. The distribution of demographic and diagnostic characteristics at baseline in the two treatment arms will be examined and described in terms of means, standard deviations, proportions and 95% confidence intervals.

5) Adjustment for covariates: Hypotheses testing will be based on models that adjust for the prespecified covariates (specifically variable medication resistance, duration of current episode and age). This adjustment will be based on the inclusion of main effects for the covariate and interactions of treatment with each of these covariates. The models that study the longitudinal trajectory of symptoms severity will include also the 2-way interaction covariate*time and the 3-way interaction terms treatment*time*covariate. Interaction terms that are not significant will be omitted. The main covariate effects will always be maintained in the models whether or not they are significant. In our experience, the association between age and medication resistance has been weak and has not presented colinearity problems. Thus, no co-linearity problems are expected with these models. All analyses performed to investigate the effect of demographic and baseline diagnostic characteristics that have been found to be imbalanced with respect to site and/or treatment group will be considered exploratory, since no a priori hypotheses are stated.

6) Statistical Rules: The conduct of new statistical analyses that have not been planned in advance will be discussed with the DSMB and must be DSMB approved.

**Hypothesis testing**

1) Primary clinical hypothesis: **Repeated daily rTMS delivered in a synchronized fashion (SYNC) over the duration of the randomized phase ("fixed" plus "variable length" components) results in superior clinical outcome compared to conventional non-synchronized (NON-SYNC) TMS.**

Primary analysis of this hypothesis will be based on the primary outcome measure remission status. A logistic regression model will model the odds for response as a function of treatment condition. The model will adjust for medication resistance, episode duration and age. If no interaction term between treatment and any of the covariates is significant, the treatment effect will be interpreted in terms of the odds ratio for remission for SYNC rTMS vs. NON-SYNC rTMS. If an interaction between treatment and any of the covariates is statistically significant, we will interpret the interaction accordingly in terms of ratio of the odds ratios for remission for SYNC rTMS vs. NON-SYNC rTMS between two different levels of the covariate factors.

We will employ additional exploratory analyses merging selected aspect from the fMRI or EEG dataset to potentially be able to predict remitters based on baseline MRI characteristics or the amount of correctly timed EEG pulses delivered.

**Approaches to Trial Conduct and Quality Control –** This study is designed to be an effectively randomized, rigorously conducted trial of SYNC versus NON-SYNC TMS for depression. It builds on and takes advantage of the infrastructure and resources in place at the MUSC BSL from prior studies, including the OPT-TMS trial.

**General Approach to Data Management –**Dr. George and the BSL members, working with other MUSC resources (e.g. SC Clinical and Translational Research Institute (SCTR)) will be responsible for data management activities of this trial. The MUSC BSL has extensive experience with all aspects of data management for single and multicenter clinical trials.

The following section describes the proposed data management plan.

**Database Creation and Documentation:** The OPT-TMS study pioneered a system at MUSC that allows for easy web-based design, validation and maintenance of the core clinical database. The database will be developed using REDCAP, working with SCTR staff and statisticians and clinical trialists. The REDCAP database will have extensive data consistency checks programmed.

**Data collection/data entry** – data is entered directly into a REDCAP database via ipad while interviewing subject. Before final locking of the database, all entries will be checked by MUSC staff. Any deficiencies are resolved via Data Clarification Requests.

**Data Quality Assurance.** Data quality will be monitored on two levels: 1) as reported on the CRF (accuracy); 2) as entered into the study database (precision). For the former, all primary, secondary and safety data will be source document verified, and all CRF's will be visually inspected by the clinical staff before archiving. In addition, extensive edit checks will be programmed into REDCAP. Finally, independent quality assurance / quality control will be performed including a 20% random sample CRF to database data listing review.

**Systems Environment and Security.** All information systems used by MUSC in the management and storage of clinical trial data are housed on site in Brain Stimulation Lab. These offices are locked during non-business hours; entry to the building from the street can only be gained through the use of the touch pad entry lock or with key for the fire exit. A regular university foot and bike patrol officer patrols the building. MUSC's software security policy has three main components. The first component is antiviral protection: Corporate Edition Version 7.5 is being used to protect all servers and workstations from infection. Virus definitions are updated on a daily basis. The second component is password policies. Oracle, Clintrial, Access and Windows all include password protection features to prevent unauthorized access. These are all activated and kept fully functional by the IS department. System and Administrator level passwords are changed on a regular basis to enhance security. In addition to anti-virus software and password protection, two levels of firewall protection comprise the third component. The Medical University of South Carolina (MUSC) maintains firewall protection between the university and outside computer systems.

**Backup Policy.** The backup schedule consists of full-verified backups performed nightly.

Reports to Designated Data Safety Monitoring Board. The Data Safety and Monitoring Board (DSMB) will receive reports produced by the BSL at 6-month intervals on study progress, efficacy, and safety. A template for the report will be submitted to the DSMB for its input. Additional study-specific information not already in the template will be incorporated into the report as requested by the DSMB.

**Randomization** will be performed automatically by a software program using an encrypted randomization table on the computer attached to the TMS machine and backed up on MUSC Box. Personnel at MUSC will have no access to this randomization table, but personnel at Columbia University, who have no contact with subjects or access to primary clinical data, will be performing ongoing quality control. The randomization application will assign to each newly randomized subject a blinded designation of SYNC or Non-SYNC. The interface computer that drives the TMS machine will then operate either in a manner that synchronizes the treatment with the patient's EEG, or delivers non-synchronized TMS (identical frequency but randomized phase

Primary Clinical data will not leave MUSC. Processed MRI and EEG, de-identified data, will be analyzed by colleagues at Columbia University. Data will be transferred using MUSC Box, with subject number only and no other identifying information. The Columbia group will not get any data other than EEG and MRI files and the research number of the participant. They will never get other protected health information.

## 13.0 Provisions to Monitor the Data to Ensure the Safety of Subjects (if applicable)

There are 3 areas in which safeguards to protect subjects from undue risk require discussion. These include the procedures used to obtain informed consent, the procedures used to ensure confidentiality of the subjects' data, and the procedures used to minimize possible risks associated with the treatment procedures.

**Informed Consent.** In the consent forms and discussions with an investigator, patients are advised fully of the procedures to be used, the amount of time required of them, the fact that this study involves random assignment to two forms of TMS, only one of which has been tried before, the nature of the study and follow-up, the research procedures that will be conducted, the possible risks and benefits of the procedures, their right to refuse participation in the study without prejudice, their right to terminate participation at any moment without prejudice, and the name and telephone number of the Principal Investigator. All subjects will be required to have capacity to consent.

**Confidentiality of Subjects' Responses.** In the informed consent form, subjects are told that the information they provide and all findings will be kept strictly confidential, with access limited to the research staff at the research sites and the possible exception of state or federal regulatory personnel. No one but the project staff has access to the master list linking subjects' names to code numbers, and all information obtained is coded. The respective master lists are kept under strict lock and key at MUSC and with restricted access in Redcap.

**Research Procedures.** We have described above the potential risks of the research procedures. If the patient shows deterioration in their clinical status, we will stop him/her from proceeding in the study, and coordinate appropriate follow-up care with the referring psychiatrist. Certified TMS operators will visually determine the motor threshold using parameter estimation by sequential testing (PEST). We will minimize the risk of seizure by prescreening patients with an MRI scan of the head, and will tailor each person's stimulation parameters to their own motor (and indirectly seizure) threshold. We will exclude patients on all psychotropic medications (except for lorazepam at no greater than 3 mg/d) and all stimulants (except for caffeine). These could potentially lower the seizure threshold. We will minimize hearing damage by having all patients wear earplugs to protect their hearing during the TMS and MRI sessions. We will minimize the anxiety due to the MRI procedure by offering patients a mirror to look outside the bore at a screen and provide continuous feedback and update of procedure to patients in the scanner. All magnetically sensitive objects such as credit cards and electronic devices such as hearing aids, watches, and calculators will be put in a container to prevent damage from the magnet. The patient will be stimulated in clinical settings designed for TMS. An Ambu bag will be available. Patients will place earplugs in their ears.

Participation in the study will be treated as confidential, as will all records. The Food and Drug Administration and Institutional Review Board will have access to the records, but patients will be assigned study numbers for record keeping purposes. We will protect the identity of our patients by keeping the data in file cabinets in the PI's locked office, to which only they have a key.

**Data and Safety Monitoring Board.** Since this proposal is an early phase Clinical Trial, we will establish a Data and Safety Monitoring Board in conjunction with NIMH staff. This DSMB will be composed of at least one statistician, one psychiatrist familiar with depression and TMS but not linked to this research group, and several others. They will meet once in person before the clinical trial starts to adopt standard procedures, elect a chair, and then will meet annually by phone to review study progress and AE's. They will also meet after the study is completed and final results are tabulated and submitted for publication. They have the authority to meet periodically as needed in addition to these planned meetings.

**Safety and Data Monitoring Plan.**

This grant application meets NIH policy and Guidelines on the inclusion of a Data and Safety Monitoring Plan for clinical trials. The patients will be fully informed of the nature of the study requirements prior to enrollment and periodically at weekly visits. The Data Safety Plan follows:

**Conduct Ongoing Monitoring.** The Study Coordinator, research nurses and other staff will be in constant communication with Dr. George regarding any adverse events that might occur. Additionally, we will have monthly executive committee phone conferences (Drs. George, Brown and Sajda) and will have time set aside for any potential complications or adverse events. Moreover, the MUSC IRB conducts frequent initial and then periodic audits to assess data quality. In addition, the DSMB will be notified for SAE's. The DSMB will review SAE's every 6 months. All SAE's will be forwarded to the IRB, FDA and NIH on a quarterly basis.

**Plans for Stop Analysis.** Because of the anticipated low level of side effects of TMS, the DSMB will be charged with reviewing side effects in year 2. Only if there is a need for determination whether a high level of side effects is due to SYNC TMS, would they be charged with breaking the randomization scheme and unblinding.

## 15.0 Risks to Subjects

**Potential risks related to TMS:** Based on previous clinical work of left prefrontal rTMS in depression, and in various other psychiatric disorders as well as others researchers published and communicated experiences, we hypothesize that NON-SYNC left prefrontal rTMS (as intended in this grant) is an effective antidepressant treatment, and that SYNC rTMS will be at least as effective or better. This study is an important necessary step to characterize the safety, and efficacy of the antidepressant effect.

**Potential worsening of depression symptoms with TMS**: Several studies have so far demonstrated the feasibility of rTMS in depression without any alarming indicators of exacerbation of symptoms. We

will work closely with the patient to familiarize them with the experimental setup. The BSL team members at MUSC are experienced with the procedure and are among the leading experts in the field of brain stimulation and TMS. We will also monitor closely for worsening suicidal ideation or increasing hypomania or mania.

**Potential risk of a seizure**: Unlike ECT, in routine use, TMS stimulates the neurons at a sub-convulsive level, although less than 50 seizures have been noted in the literature. Six of them have been in healthy volunteers (without any history of seizures, brain masses or traumatic brain injuries). The risk of seizure induction is related to the intensity, duration, frequency and rest interval of stimulation. Following the adoption and widespread use of the safety guidelines from an NINDS workshop on TMS, 10 seizures have been reported since 1997 and they involved parameters of "higher settings" then the "safe range" [19-21], or interactions of TMS with medications known to lower the seizure threshold. To our knowledge, stimulation with the parameters and settings we propose to use does not cause seizures, even the SYNC settings. We will carefully titrate each person's stimulus intensity to his or her motor threshold, before beginning treatment. Our study patients will be off neuroleptics and other psychotropic medications for at least 2 weeks (except benzodiazepines).

**Other potential effects of TMS on brain tissue:** TMS is thought to be safe, with no brain damage, despite extensive use in humans and other animals [22-32]. We have recently completed a case report of a "maintenance treatment of rTMS for depression over a year, where a depressed patient received a total of ((16,000 x 2 trials) + (8,000 x 12 trials)) = 32,000 + 96,000 = 128,000 stimuli over a year period. The patient's MRI showed no structural changes at the end from baseline. The patient experienced no seizures and had tolerated the procedure equally throughout the successive trials.

We have also reported a safety study [33] looking at the MRI scans before and after 2 weeks of daily left prefrontal rTMS for depression. Specifically, we found no structural changes in left prefrontal lobe of patients who received active rTMS compared to placebo. We have also performed an MRI diffusion imaging study before and after TMS/fMRI study (similar to the one proposed here) and found no deleterious effect of TMS on brain tissue at the site of stimulation. [34]

**Potential hearing loss.** The discharge of the rTMS coil generates a high-energy click that may cause cochlear damage. Humans exposed to rTMS have shown temporary increases in auditory threshold (especially at high frequencies) lasting at least 5 minutes and less than 4 hours[22, 35]. Foam earplugs can protect against these changes and will be worn by the patients and the researchers present during TMS sessions.

**Potential changes in cognitive function:** There have been no reports of long-term changes (more than a minute) in cognitive function (memory, attention, etc) in rTMS studies. Safety studies specifically looking for these changes did not find any effects of rTMS with the exception of one open study in which healthy volunteers were exposed to 150 trains of rTMS at different site of stimulation in a paradigm that lasted more than 3 hours [36]. There was a significant decrease in scores on a logical memory test. The stimulation parameters exceeded the recommended safety range and there was no control for patient fatigue or other non-specific effects. In numerous antidepressant studies with TMS, there have been no deleterious effects, and in fact patients scored higher after TMS, likely due to the TMS unburdening them of their depression, which temporarily worsened their cognitive scores. [37, 38]

**Safety in case of pregnancy:** This protocol will exclude pregnant women (women of child bearing age will perform a pregnancy test prior to enrollment)

**Potential risks related to MRI scanning.** There are very few potential risks from MRI itself. There is no exposure to ionizing radiation and the machine and scanning sequences and gradients are approved by the FDA for routine clinical use.

**Metallic objects:** If a patient has any metal implants (not including dental fillings), a pacemaker, or other irremovable medical devices, the patient would be at risk from the device or implant shifting during the scanning procedure but the patient will be asked to inform the study investigators about these at the beginning of the study and again prior to scanning so that they won't be scanned. If a patient has a removable metal object on his body then it may propelled by the MRI magnet, causing injury. To minimize this risk, patients will be asked and inspected for any evidence of metal objects that might cause harm in the scanner and such objects will be removed prior to scanning.

**Claustrophobia due to MRI scanning:** If a patient is claustrophobic, the MRI scanning procedure might cause anxiety. We will work with the patient to minimize the effect of anxiety. Patients

will be given the option of prism glasses that allows them to look outside. We have found that a regular communication with the patients while in the scanner and updating them of the progress of the experiment (calibration, shimming and tuning, getting the structural scans), is also extremely helpful in minimizing the anxiety level. The PI's and their neuroimaging colleagues have extensive experience in imaging patients with mood disorders during structural and even longer lasting functional paradigms[39].

**Hearing loss:** A patient may experience some loud noises during the MRI scanning procedure and there is a mild risk of hearing damage if patients are not given protective earwear. Patients will be using sound-dampening headphones and wearing earplugs to decrease the intensity of these noises and minimize this risk.

## 16.0 Potential Benefits to Subjects or Others

**Summary of Risk Analysis.**
The potential benefits of this study outweigh the risks for both patients and controls.
For the individual depressed subject. Depressed patients who have failed to respond to medication are at risk of suicide and prolonged disability. Daily left prfrontal rTMS for 4-6 weeks has antidepressant effects. One arm of the study involves conventional TMS and many patients will get relief from their depression. The experimental arm (SYNC) will likely also result in depression remission, but perhaps at a lower rate. Or perhaps higher. But all patients enrolled have a significant chance of getting their depression treated.
For society. The risks of the rTMS listed above are slight relative to electroconvulsive therapy, a treatment often used in this population. If this trial is successful and SYNC rTMS proved to be a more effective alternative to NON-SYNC TMS, depressed patients not responding to medication would have a better treatment alternative that might begin to compare with ECT in terms of acute remission rates, with fewer side effects and risks. The protocol is safe, and the potential benefit to society of improving a safe tool as a potential treatment modality for depression is enormous and well worth the potential risk involved in this protocol.

## 17.0 Sharing of Results with Subjects

At the formal completion of the entire clinical trial after all data have been reviewed and the dataset locked, we will be able to let subjects know whether they received the SYNC or NON-SYNC TMS. This may be helpful if they require additional TMS in the future.

## 18.0 Drugs or Devices (if applicable)

Daily left prefrontal rTMS for treating depression has been FDA approved since 2008. Thus an IDE is not needed for this population and this trial. We will need to use a TMS system that uses a figure eight coil, like the one we are using in the MRI scanner. There is one TMS coil that was FDA approved for treating depression in 2013 (Brainsway). Unfortunately, it is not possible to put this coil in an MRI scanner. Moreover its magnetic field properties are likely much different than the standard figure eight. As the Brainsway coil has a wider and deeper field, it might produce circuit changes that are widely varying from what we are testing in the R21 phase.

We will thus follow the pattern we used in the OPT-TMS trial to select an appropriate industry partner. We are using a Magstim Horizon TMS system. The industry partner will not be involved in the trial in any other way, other than having to know about SAE's for FDA reporting. They will be able to refer to the trial as having been conducted with their machine.

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