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Safety and Feasibility of Accelerated Low-Frequency Transcranial Magnetic Stimulation for Medication-Resistant Depression in Patients with Epilepsy

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List of Abbreviations

DLPFC – Dorsolateral Prefrontal Cortex
EEG – Electroencephalogram
EPs – Evoked Potentials
IAPS – International Affective Pictures Set
LF TMS – Low Frequency Transcranial Magnetic Stimulation
MINI - Mini-International Neuropsychiatric Interview
MOCA - Montreal Cognitive Assessment
MT - Motor Threshold
PANAS - Positive and Negative Affect Schedule
QIDS – Quick Inventory of Depressive Symptomatology-Subject Rated and Visual Analog Scale
QOL – Quality of Life
SAFTEE – Systematic Assessment for Treatment Emergent Events
TLE – Temporal Lobe Epilepsy

Study Summary

Title	*Safety and Feasibility of Accelerated Low-Frequency Transcranial Magnetic Stimulation for Medication-Resistant Depression in Patients with Epilepsy*
Short Title	*TMS for Depression in Patients with Epilepsy*
Protocol Number	*N/A*
Phase	*Phase 2*
Methodology	*Non-randomized, non-controlled*
Study Duration	*11/1/2015 – 10/31/2020*
Study Center(s)	*DHMC, Lebanon, NH* *DHMC, Manchester, NH (Recruitment)*
Objectives	*Primary objective is to determine whether it is safe and feasible to administer low-frequency right frontal lobe transcranial magnetic stimulation using an accelerated protocol to treat depression in patients with focal epilepsy.*
Number of Subjects	*20*
Diagnosis and Main Inclusion Criteria	*Epilepsy and moderate symptoms of depression*
Study Product, Dose, Route, Regimen	*MagVenture transcranial magnetic device with a figure 8 coil, delivered in 15 50-minute trains of 1 Hz; 45,000 total pulses; stimulation intensity between 80-120% of patient's motor threshold*
Duration of administration	*3 days*
Reference therapy	*None*
Statistical Methodology	

1 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Background

The International League Against Epilepsy defines epilepsy as a disorder of the brain characterized by: (1) an enduring predisposition to generate epileptic seizures; and (2) the neurobiological, cognitive, psychological, and social consequences of this condition[1]. The 2012 Institute of Medicine Report on Epilepsy proposes that treatment of epilepsy should not only focus on seizures, but also on its comorbidities[2]. In response, the National Institute of Neurological Disorders and Stroke (NINDS) established Epilepsy Research Benchmarks, including: Area III: Prevent, limit, and reverse the comorbidities associated with epilepsy and its treatment[3]. Epilepsy comorbidities include several somatic, psychiatric, and cognitive disorders that contribute to the adverse impact of the disease.

The most frequent psychiatric disorder comorbid with epilepsy is depression which is present in approximately 20% of patients[4] and includes patients with both focal epilepsy[5, 6] and idiopathic generalized epilepsy[7, 8]. Patients with epilepsy and depression have significantly decreased quality of life[9] and have increased use of costly medical resources[10]. Despite this, very little research has focused on the effective treatment of depression in epilepsy patients. Critically, about 30% of persons with epilepsy and MDD do not adequately respond to standard pharmacological therapy for treating depression. For patients with medication-resistant depression, there are no quality data to guide treatment.

The manifestations and diagnosis of depression in patients with epilepsy may differ compared to depression occurring in patients without epilepsy. Studies confirm that most frequently depression manifests similarly in patient with epilepsy and without epilepsy fulfilling criteria for DSM major depression disorder [11-13]. However, compared to the general population patient with epilepsy often have more chronic dysthymic course with milder symptoms and fewer fluctuations [14]. Studies show that significant number of patient with epilepsy fail to meet a specific DSM Axis 1 diagnosis for MDD despite self-reporting depression of mild to moderate severity on the Beck Depression Inventory[15].

The etiology of MDD in patients with epilepsy has been controversial with opinions divided between theories of psychosocial versus biological factors. The psychosocial argument highlights the high rates of unemployment, lower rates of educational achievement, lower rates of marriage, higher rates of divorce, relative social isolation, and stigma in patients with focal epilepsy, and temporal lobe epilepsy in particular. In contrast, nearly 30 years of imaging studies have identified numerous abnormalities in brain regions in patients with MDD, including those with focal epilepsy and MDD. Patients with MDD have been shown to have decreased gray matter volume in the frontal lobes, amygdalohippocampal complex and the anterior cingulate[16-18]. Studies in patients with certain types of focal epilepsy and comorbid depression have identified correlations between severity of depression and degree of hypometabolism on PET and cortical thickness on structural MRI in the orbitofrontal cortex, as well as hippocampal and amygdala volume[19-25]. These imaging studies provide strong evidence for a neurobiological basis of depression in patients with focal epilepsies.

In addition to studies using PET and MRI in patients with MDD without epilepsy, investigators have searched for EEG based biomarkers. Higher power in the alpha frequency band defined as 8-12 Hz in the left frontal lobe has been robustly reproduced[26-34]. In addition, theta frequency activity ranging between 4-8 Hz which has been conceptualized as the frequency of communication between cortical areas has been shown to be lower in patients with MDD in the temporal and prefrontal regions and in the cingulate region using dense array EEG techniques[33, 35, 36]. While at Emory, Dr. Holtzheimer's group showed that prefrontal theta power predicted the antidepressant response to deep brain stimulation in patients with highly treatment-refractory depression[37]. Furthermore, more recent studies measuring functional connectivity using dense array EEG source modeling demonstrated elevated coherence between frontal and temporal alpha in MDD[38].

1.2 Investigational Agent

Repetitive transcranial magnetic stimulation (TMS) is a nonpharmacological, noninvasive method for stimulating the brain and modulating neural network activity. TMS has shown potential benefit in treating a number of neuropsychiatric disorders, especially depression[39]. With TMS, an electromagnetic coil placed against the scalp is used to generate a rapidly changing, relatively high strength magnetic field (~2 Tesla) that passes unimpeded through scalp and skull and generates an electric current in the underlying cortex. Using current "figure of eight" coils, stimulation can be focused to a 2-3 cm diameter region of cortex, allowing relatively focused stimulation. Due to the rapid decrease in magnetic field strength with distance from the coil, stimulation is generally limited to surface cortical stimulation (e.g., sensorimotor cortices, surface prefrontal cortices). TMS has been investigated as a diagnostic and therapeutic approach for several neuropsychiatric conditions including depression, schizophrenia, obsessive-compulsive disorder, addiction, epilepsy, and parkinsonism.

High-frequency (HF) TMS refers to TMS delivered at a frequency at 5 Hz or above. HF TMS applied to the left dorsolateral prefrontal cortex (DLPFC) is an FDA-approved treatment for medication-resistant depression and is becoming widely available in the community. Left HF DLPFC TMS has established clinically and statistically significant antidepressant effects[40]. However, HF TMS can increase cortical excitability and is associated with an increased risk of seizure[41]. As such, use of FDA-approved depression treatment protocols in patients with epilepsy would be relatively contraindicated, and there has been reluctance to study TMS in patients with epilepsy. Despite this potential increased risk of seizures, at present time the actual risk of a patient with either focal or generalized epilepsy experiencing a seizure during the course of treatment with TMS has not been studied. In addition, there is no evidence to suggest that patient with focal epilepsy or generalized epilepsy differ with regards to the risk of potential seizures by high frequency TMS.

Low-frequency (LF) TMS refers to TMS delivered at a frequency of 1 Hz or below. Unlike HF TMS, LF TMS can decrease cortical excitability and may have anticonvulsant effects[42]. Low frequency TMS applied to right DLPFC also has an extensive though smaller database supporting its antidepressant efficacy, and comparisons to left HF DLPFC TMS suggest both treatments work equally as well[43, 44]. Surprisingly, LF TMS has not been investigated as an antidepressant treatment in patients with epilepsy, though it would have clear advantages compared to HF TMS including increased tolerability and potentially anticonvulsant effects.

The mechanism of action of TMS is not fully known. As HF and LF TMS respectively increase and decrease cortical excitability of the underlying cortex, these local effects likely comprise some of the mechanism. Converging data strongly support a role for the dorsolateral prefrontal cortices in the pathophysiology of depression, and a common abnormal pattern is left-right imbalance in activity characterized by relatively lower left DLPFC activity (e.g., decreased blood flow or metabolism; increased alpha power) and relatively higher right DLPFC activity[30, 45-49]. A simple hypothesis is that TMS works by either "turning up" activity in the left DLPFC versus "turning down" activity in the right DLPFC. One measure of prefrontal cortical activity is alpha power derived from a resting state scalp EEG. Thus, patients with focal epilepsy and comorbid depression would be expected to have left-right asymmetry in prefrontal alpha power. Further, LF TMS to the right DLPFC would be expected to alter prefrontal alpha power asymmetry which may correlate with antidepressant efficacy associated with this intervention. As above, the effects of TMS on prefrontal theta power and prefrontal-temporal alpha coherence may also be involved in the antidepressant mechanisms of TMS.

1.3 Preclinical Data

No available non-clinical data is available.

1.4 Clinical Data to Date

Repetitive transcranial magnetic stimulation (TMS) is a non-pharmacological, non-invasive, non-convulsive method for stimulating the brain and modulating neural network activity. High frequency (HF) TMS applied to the left dorsolateral prefrontal cortex (DLPFC) is an evidence-based, FDA-approved antidepressant treatment[39]. However, due to the potential for HF TMS to induce unwanted seizures in susceptible patients (e.g., those with epilepsy), this treatment has never been assessed as a treatment for TRD in patients with epilepsy. Low frequency (LF) TMS of the right DLPFC has also been shown to have antidepressant efficacy and may actually be anticonvulsant; surprisingly, this intervention has never been evaluated as an antidepressant intervention in patients with epilepsy.

1.5 Dose Rationale and Risk/Benefits

Low-frequency (LF) TMS refers to TMS delivered at a frequency of 1 Hz or below. Unlike HF TMS, LF TMS can decrease cortical excitability and may have anticonvulsant effects[42]. Low frequency TMS applied to right DLPFC also has an extensive though smaller database supporting its antidepressant efficacy, and comparisons to left HF DLPFC TMS suggest both treatments work equally as well[43, 44]. Surprisingly, LF TMS has not been investigated as an antidepressant treatment in patients with epilepsy, though it would have clear advantages compared to HF TMS including increased tolerability and potentially anticonvulsant effects.

2 Study Objectives

Specific Aim 1: To examine the safety and feasibility of accelerated low-frequency transcranial magnetic stimulation (TMS) to the right dorsolateral prefrontal cortex in patients with epilepsy and comorbid depression.

Hypothesis 1.a. (safety): Treatment will not produce serious adverse events defined as an increase in seizure rate or hospitalization.

Hypothesis 1.b. (safety): Treatment will not be associated with a higher rate of adverse events as measured by a modified Systematic Assessment for Treatment Emergent Events (SAFTEE) given at baseline and immediately post-TMS.

Hypothesis 1.c. (feasibility): At least 80% of participants will complete the study protocol.

Specific Aim 2: To examine the utility of electrophysiological and behavioral profiles as biomarkers of depression correlated with response to treatment with right-DLPFC TMS in patients with epilepsy.

Hypothesis 2a: Changes in dense array EEG based biomarkers of depression (hemispheric frontal alpha power asymmetry, anterior cingulate theta power, and frontotemporal alpha coherence) will correlate with changes in depression scores.

3 Study Design

3.1 General Design

This protocol is for a pilot study designed primarily to assess whether patients with epilepsy can safely tolerate low-frequency transcranial magnetic stimulation in an accelerated protocol to treat depression. We aim to enroll 20 patients with epilepsy and comorbid depression to receive a total of 14 hours of transcranial magnetic stimulation over 3 days at DHMC - Lebanon. We will assess safety of this protocol with regards to seizure frequency and other side effects of TMS treatment and the feasibility of using an accelerated protocol in this patient population. In addition to these primary aims, our secondary goal is to determine if dense array EEG can provide a useful biomarker for depression and its treatment in epilepsy. We will obtain a structural MRI before treatment and a dense array EEG before and after TMS treatment to assess for changes in specific dense array EEG based biomarkers. We will obtain a function MRI before treatment , and a dense array EEG before and after TMS treatment. Subjects will complete a brief battery of neuropsychological testing

before and after the treatment to assess for any changes in social cognition or executive functioning that may result from TMS or the change in depressive symptoms.

In addition to recruiting patients, we will likewise recruit family members or friends of the patient and ask them to monitor the patient for side effects to TMS treatment. The recruited family member will bring the patient to the treatment and stay with the patient overnight at a local hotel and monitor for possible seizures or other adverse events of treatment. Family members will be instructed in seizure safety and be given emergency phone numbers to call if the patient is experiencing adverse effects of TMS. When feasible, patients and their family members will be given the option to commute to the medical center on treatment days rather than staying in a local hotel.

3.2 Primary Study Endpoints

1. Change in weekly seizure rate as assessed by self-report seizure log.
2. Change in significant side effects as assessed by the Systematic Assessment for Treatment Emergent Events (SAFTEE)[50].
3. Feasibility of participation such that 80% of patients will complete the study protocol including all measures, MRI, dense array EEG, and TMS.
4. Correlation of pre and post TMS hemispheric frontal alpha power asymmetry, anterior cingulate theta power, and frontotemporal alpha coherence with changes in depression severity.

3.3 Measures

The following measures will be assessed at various time points over the course of the study (see Table 1):

- Mini-International Neuropsychiatric Interview (MINI): Designed for use in clinical trials, the MINI is a validated, structured diagnostic interview which can be administered by non-specialized interviewers. The interview takes approximately 15 minutes to administer, and allows clinicians to diagnose psychiatric disorders according to DSM-V and ICD-10 criteria.
- Montreal Cognitive Assessment (MoCA)[51]. The MoCA is a validated screening tool for mild cognitive impairment. The brief screening takes approximately ten minutes and can be administered by trained interviewers. Results can only be interpreted by a trained health care professional.
- Positive and Negative Affect Schedule (PANAS)[52]. The PANAS is a 20-item test that measures both positive and negative affect. It has been strongly validated with measures of state anxiety, distress, and depression.
- Quick Inventory for Depressive Symptomatology-Subject Rated (QIDS)[53]. The QIDS is a validated and reliable measure of the intensity of depressive symptoms. This 16-item self-report form takes approximately five minutes to administer.
- Systematic Assessment for Treatment Emergent Events (SAFTEE)[50] The 55-item SAFTEE was designed for the detection of side-effects in clinical trials
- MRI Screening Form: A standard form assessing safety of MRI for the patient. Modification will include question about prescription eyeglasses for fMRI adjustments.
- Antidepressant Treatment History Form: A self-report checklist of current and past anti-depressant medication use.
- Quality of life in epilepsy (QOLIE-31): The QOLIE-31 is a 31-item survey used to assess the health-related quality of life factors in adults (18 years and older) with epilepsy. This scale has been validated and is considered to be reliable.
- Memory Assessment Clinics Self-Rating Scale (MAC-S)[55]: This validated and reliable, self-rated questionnaire is to assess how individuals remember specific information.

- The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): The RBANS is a valid and reliable neuropsychological battery that assesses five different domains and

includes twelve subtests. The five domains include immediate memory, visuospatial/constructional, language, attention, and delayed memory.

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4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

Participants will be recruited from the epilepsy patient population within the Department of Neurology at Dartmouth-Hitchcock Medical Center. Screening and baseline evaluations will be performed by a board-certified neurologist and psychiatrist as well as a research coordinator trained to reliably administer structured interviews and rating scales. 20 participants will be recruited with the following initial inclusion criteria:

- Females or males age 18 and older.
- Able and willing to provide informed consent.
- Diagnosis of probable epilepsy (focal or generalized) confirmed by the study neurologist.
- English-speaking
- Not pregnant
- Able to safely undergo MRI (as assessed by MRI safety form).
- Have a family member or friend (proxy) who will be able to bring the patient to the hospital and serve as a safety monitor for two consecutive nights.
- Patients on stable doses of current antiepileptic and antidepressant medications for 1 month.

Once patients fulfill initial inclusion criteria, they will be referred to see the study psychiatrist who along with a research coordinator will determine if patient meets the following further inclusion criteria:

- Diagnosis of a depressive episode of any severity (including, mild, moderate, and severe) by the study psychiatrist (Quick Inventory of Depression Severity-Subject Rated [QIDS] score >6 or Neurologic Disorders Depression Inventory – (NDDI-E) score of > 15.
- Inadequate response to at least one antidepressant medication during the current episode.

Exclusion Criteria

Patients will be excluded if the following criteria are met:

- Significant cognitive impairment (Montreal Cognitive Assessment [MOCA] <23)
- History of other major psychiatric disorders (e.g., schizophrenia, bipolar disorder,) or presence of unstable medical comorbidities, which the investigators agree, will interfere with adherence and/or safety.
- Active substance use disorder that the investigators agree will interfere with adherence and/or safety.
- Actively/imminently suicidal (QIDS item 12 score > 2 or MINI Suicidality module score > 16)
- Greater than 10 seizures per week during 1 month prior to treatment, confirmed by the study neurologist.
- History of stroke, moderate-severe traumatic brain injury or other major neurological disorder, which the study neurologist feels will interfere with adherence and/or safety.
- Any magnetic or implanted device that will interfere with ability to safely receive MRI and/or TMS treatment.

4.2 Subject Recruitment and Screening

Participants will be recruited from the epilepsy patient population within the Department of Neurology at Dartmouth-Hitchcock Medical Center Lebanon and Manchester. Initial screening (and consent) will be performed by study neurologist or designee at either of the Lebanon or Manchester locations.

Once a patient is identified as fulfilling initial inclusion criteria they will be referred to be seen by study psychiatrist (or qualified designee) who will determine final eligibility.

4.2.1 When and How to Discontinue Treatment

Treatment will be discontinued and the subject may be withdrawn from the study prior to completion due to any of the following reasons:

1. The subject experiences greater than 3 typical seizures during the 3 day course of TMS treatment or they experience a single atypical seizure (atypical duration or severity for the patient) as judged by study neurologist.
2. The subject experiences a worsening of depressive symptoms by the discretion of the study psychiatrist.
3. The subject withdraws consent.
4. The subject is not able to tolerate TMS (as assessed by self-reported side effects).
5. The subject does not adhere to protocol requirements.

4.3.2 Data Collection and Follow-up for Withdrawn Subjects

Should a subject be withdrawn prematurely from the study, follow-up will continue to be attempted as planned based on protocol: subjects will complete assessments immediately following discontinuation of TMS, one week after last TMS treatment, one month after last TMS treatment, and three months after last TMS treatment. For a subject to be considered "lost to follow-up," they must at a minimum fail to respond to 3 consecutive attempts at communications from study team (email and phone contact). Follow-up will not occur if a subject refuses to participate in follow-up assessments.

5 Study Device

5.1 Description

Figure 1 MagVenture MagPro TMS device setup to provide left TMS treatment. This device is also capable of providing right TMS treatment as proposed in this study.

TMS Device

Repetitive transcranial magnetic stimulation (TMS) is a focal, nonpharmacological, noninvasive method for stimulating the brain and modulating neural network activity. To administer TMS, an electromagnetic coil is placed on the scalp, and uses electrical current to create magnetic fields that depolarize or hyperpolarize neurons in the brain. See attached manual for more information regarding the MagVenture TMS device.

TMS will be delivered at 1 Hz over the course of fifteen 50-minute trains, for a total of 45,000 pulses. Four trains will be planned for day 1, with no more than five trains occurring on day one. Seven trains will be planned for day two, and four trains will be planned for day three. No more than seven trains will be delivered on any one day, and the treatment will occur over no more than four days. If the fifteen trains are not completed by the end of the third treatment day, subjects will have the option of returning for a fourth day to complete the remaining trains. Stimulation intensity will be set to 80% of the individual's motor threshold (the lowest energy output of the machine needed to evoke a motor response in the small muscles of the left hand) for the first several stimuli of the first session. The intensity will be steadily increased in regular intervals during the first session until reaching 120%. If higher intensity stimuli are not tolerated (due to discomfort or misplacement of the stimulus), then treatment will be continued at a lower intensity until the following session. During the following session, stimulus intensity will again be sequentially increased to 120%.

MRI

Magnetic resonance imaging (MRI) will be performed using a 3T Philips Intera Achieva scanner (Philips Medical Systems, Best, The Netherlands) with a 32-channel head coil. High-resolution anatomic images

will be acquired at 1x1x1.2 mm^3 resolution with an MPRAGE sequence (FOV 256x240x204 mm^3, TR shortest, TE shortest, FA 8°, SENSE factor 1). Patients will receive a resting, structural scan. . Anatomical data will be used for EEG analyses as described below.

Dense Array EEG

EEG will be performed using the Electrical Geodesic EEG System 400 dense array recording device with 256 electrodes (Electrical Geodesics, Inc., Eugene, OR). The Geodesic Photogrammetry System will be used to obtain the precise location of all electrode contacts in combination with structural MRI data. Resting EEG data will be acquired with eyes closed. Patients with epilepsy and depression will have EEG performed prior to and following the accelerated TMS course and then at the follow-up visits (Visits 7 and 9).

Pre-processing of EEG data will be performed using Net Station 4.5 (Electrical Geodesics Inc., Eugene, Oregon). The coordinates of each electrode will be corrected for each patient based on the pictures taken by the geodesic dome preceding the EEG recording. Artifact detection will be performed to mark all EEG segments containing eye and head movements or muscle artifacts. The EEG data will be band-pass filtered between 0.5 and 70 Hz. T1 MRI images for each patient will be segmented in FreeSurfer and imported into Brainstorm, a Matlab-based program dedicated to EEG data analysis. In Brainstorm, a head model will be created and each patient's electrode coordinates will be imported/co-registered with the T1 MRI images. For each subject, the EEG signals will be analyzed in 84 regions of interest (ROIs) defined according to the 42 Brodmann areas (BAs) for left and right hemispheres [49]. These ROIs could be defined for each subject using FreeSurfer. Low resolution electromagnetic tomographic analysis (LORETA), which could be used to localize cortical and subcortical sources from where EEG signals generates, will be used to inversely estimate the EEG signal from these ROIs. The EEG data will be investigated in the following aspects: 1) frequency content, including composition of delta (0.5-3 Hz), theta (3-7 Hz), alpha (7-13 Hz), beta (13-30 Hz), and gamma (>30 Hz) EEG oscillations along with their percent ratio; and 2) spatial heterogeneity, including global functional connectivity and interhemisphere asymmetry in above-mentioned frequency bands.

5.2 Method for Assigning Subjects to Treatment Groups

All 20 patients with epilepsy and depression will be enrolled into the treatment group. All patients will have dense array EEG and MRI.

5.3 Subject Compliance Monitoring

Because a research RN or a trained TMS study team member will deliver the TMS treatments, treatment compliance will be monitored throughout administration. The RN or study team member will ensure that the subject does not fall asleep during the treatment sessions.

5.4 Prior and Concomitant Therapy

Subjects past antiseizure medications will be obtained from the medical history. Subjects antidepressant medication/treatment history will be obtained at screening using the Antidepressant Treatment History Form. Subjects may remain on a stable dose of their antidepressant and anti-seizure medications during the study. No antiepileptic or anti-depressant medication changes during the study will be allowed unless medically necessary.

5.5 Blinding of Study Device

Neither the patient nor the physician will be blinded and all patients will receive treatment.

6 Study Procedures

Recruitment and initial screening by the study Neurologist may take place at DHMC- Manchester. All other study visits will take place at Dartmouth-Hitchcock Medical Center (DHMC) in Lebanon, NH.

6.1 ***Visit 1a: Initial Screening by Neurologist – Pre-enrollment***

- Patient will review and sign informed consent.
- Initial screening will be done by a board-certified neurologist (, Visit 1a). Patient's history and physical will be taken, medications will be reviewed, seizure log, MOCA will be performed if time permits. All incomplete assessments may be done at Visit 1b.
- Subject will receive seizure log and instructions for its use.

6.2 *Visit 1b: Initial Screening by Psychiatrist – Pre-enrollment*

- Subsequent evaluation will be done by board-certified psychiatrist and research assistant Visit 1b). If the subject is unable to complete the full screening during Visit 1a, he or she may be scheduled for a second screening appointment with study psychiatrist and research assistant. At that time, diagnosis of medication-resistant depression will be confirmed; the MINI, QIDS, SAFTEE, PANAS MRI safety, TASS and ATHF will be performed. Seizure log data will be obtained.
- If time permits, Visit 2 procedures can be done at Visit 1b.

6.3 *Visit 2: Imaging and Baseline Neuropsychological Testing – Pre Enrollment*

- Patient will be report to the Advanced Imaging Center for MRI. MRI will last approximately one hour.
- After MRI is complete, patient will be brought to the EEG lab . A dense-array EEG will be conducted which will take approximately one hour.
- Patient will do neuropsychological and social-cognition testing, which will last approximately 2 hours. (QOLIE-31,RBANS and MAC-S)
- If time permits, TMS motor threshold may be done at Visit 2, so long as TMS treatment is scheduled to begin within one week. Otherwise, TMS motor threshold will be done at Visit 3.

6.4 *Visit 3: Enrollment and first day of TMS treatment*

- Patient will be brought to DHMC by their proxy for the first day of TMS treatment.
- Research staff will administer the QIDS, SAFTEE, and PANAS. Data will be obtained from the patient's seizure log.
- Patient will be given TMS motor threshold test to calibrate the machine for treatment, if not done at Visit 2. Following calibration,the designated TMS trained study team member or study RN will begin administering the first TMS treatment session under supervision of the study psychiatrist . Each treatment session will last approximately 50 minutes, and the patient will be given the opportunity to take a break between sessions. The patient will be scheduled to receive four, and may receive as many as seven, treatment sessions by the end of Visit 3.
- Following the final TMS session, study personnel will administer the SAFTEE, and PANAS.
- Following TMS, the family member/proxy will be instructed how to monitor the patient for safety, and he or she will be given contact information in case of unusually strong seizures. A hotel room will have been booked by study personnel prior to the study visit, if needed. The proxy will stay in the same room as the patient between all treatment days.
- The study Neurologist will be on call in case of unusual seizures.
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6.5 *Visit 4: Second day of treatment*

- The proxy will bring the patient back to DHMC, and report to the Psychiatry Clinic for Visit 4.
- Research staff will administer the SAFTEE and PANAS. Seizure log will be reviewed.
- After completing assessments, the subject will begin the planned seven treatment sessions. Break times will be provided between sessions if desired.
- At the end of the final treatment session, research staff will:
    - Administer the SAFTEE and PANAS.
    - Remind the patient and proxy about contact and safety information before they depart.
- The study Neurologist will remain on call in case of unusually strong seizures.

6.6 *Visit 5: Third day of treatment*

- The proxy will bring the patient back to the Psychiatry Clinic for Visit 5.
- Research staff will administer the SAFTEE, PANAS. Seizure log will be reviewed.
- The patient will have four planned treatment sessions, but may receive as many as seven treatment sessions, with the opportunity to rest between trains.
- Once the final TMS treatment session is complete, a second dense-array EEG test will be conducted, which will last approximately one hour.

- After completion of the dense-array EEG, research staff will:
  - Administer the SAFTEE, PANAS, QIDS, and MoCA.
  - Debrief patient and proxy. Provide with safety information.
- Patient will be taken home by proxy*.

*If the subject has not completed the 15 treatment sessions by the end of Day 3, they will be given the option to return to the TMS clinic for one more day to receive the remaining TMS treatment.

- The study Neurologist will remain on call in case of unusually strong seizures.

6.7 Visit 6: 1-week follow up

- After 1 week – and within 2 weeks of Visit 5, the patient will be contacted by a research staff member over the phone. Research staff will administer the QIDS and SAFTEE in addition to checking the patient's seizure log.

6.8 Visit 7: 1-month follow up

- 1 month after visit 5 (+/- 2 weeks), the patient will return to DHMC for a follow up with the study neurologist for history and physical, and medication review. Seizure log will be reviewed.
- The patient will have the SAFTEE, QIDS, and MoCA administered by research staff.
- Neuropsychological testing (QOLIE-31, MAC-S, RBANS),
- Dense-array EEG test will be conducted.

6.9 Visit 8: 3-month follow up

- 3 months after visit 5 (+/- 4 weeks), the patient will be contacted by a research staff member over the phone.
- Research staff will administer the QIDS and SAFTEE in addition to checking the patient's seizure log.

6.10 Visit 9: 6-month follow up

- 6 months after Visit 5 (+/- 4 weeks) the patient will return to DHMC for a follow up with the study neurologist, coordinator, and psychiatrist.
- Research staff will administer the MoCA, QIDS, and SAFTEE. Seizure log will be reviewed.
- Neuropsychological testing (QOLIE-31, MAC-S, RBANS) will be done by research staff.

- Medication review will be done with patient or through review of electronic medical record.
- A dense-array EEG test will be conducted, which may include EEG tasks.

7 Statistical Plan

7.1 Statistical Methods

The study will be closely monitored for safety parameters with stopping rules as defined in Section 8.7. At the conclusion of the study, baseline demographics and clinical characteristics will be summarized with means, proportions and associated standard deviations. For safety, occurrence rates of SAE (seizures or hospitalizations) will be estimated and exact binomial confidence intervals will be formed. Very few if any are expected in this small study. The SAFTEE scale will be compared before and after TMS with independent t-tests based on the individual changes from baseline. The study completion rates will be estimated and compared to the target rate of 80% using exact tests for binomial data.

The secondary outcomes will be measured before and after treatment using dense-array EEG biomarkers and depression scores along with test results during functional MRI and EEG. Paired t-tests will be used to compare *change* in depression severity, memory, executive functioning, quality of life, and social cognition from baseline to endpoint. MRI patterns of activation will be analyzed. Analysis of variance for repeated measures will be used to test task and neuropsychological testing results.

7.2 Sample Size Determination

For the primary safety outcomes, we consider the expected upper limit of a one-sided 90% exact confidence interval for the proportion with an SAE based on a sample size of 20. If the underlying rate is 0.05, the upper limit is 0.131. This increases to 0.145 if the underlying rate is 0.10.

For the secondary outcomes comparing baseline to endpoint depression measurements, a two-sided paired t-test with a significance level of 0.05 and a power of 0.90 can detect a difference of .764 standard deviations of the changes from baseline.

7.3 Subject Population(s) for Analysis

The patients successfully initiating the trial will be the analysis population to the safety outcomes. The patients completing the TMS will be the population for the secondary outcomes.

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets <u>all</u> of the following criteria:

- <u>Unexpected in nature, severity, or frequency</u> (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc.)
- <u>Related or possibly related to participation in the research</u> (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- <u>Suggests that the research places subjects or others at greater risk of harm</u> (including physical, psychological, economic, or social harm).

Adverse Event
An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Adverse Event Reporting Period
The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment. After 30 days, only adverse events related to an increase in seizure frequency or symptoms of depression will be reported.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Abnormal Laboratory Values
A clinical laboratory abnormality should be documented as an adverse event if <u>any one of the following</u> conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2 Notification and Recording of Self Harm as Indicated by the MINI and/or QIDS

Subjects will complete a series of assessments several times during their participation in the study. Two of the assessments, the MINI and the QIDS, are validated measures of depression. On the QIDS, participants are asked to select a response that best describes how they have been feeling in the past seven days. Item 12 asks about "Thoughts of Death or Suicide." This particular question will be reviewed by study personnel each time the subject completes the QIDS. Each time a subject responds positively to this question by selecting a 2 ("I think of suicide or death several times a week for several minutes.") or a 3 ("I think of suicide or death several times a day in some detail, or I have made specific plans for suicide or have actually tried to take my life.") the following procedure will be followed by study personnel:

1) Administer the Columbia Suicide Severity Rating Scale (C-SSRS).
2) Notify the study psychiatrist and an appropriate clinician (if needed) for assessment.
3) In REDcap, under **Safety Reporting,** document that the subject gave this answer, when the answer was given, and the clinician(s) notified.
4) The notified clinician may follow up with the subject and take appropriate action according to the unique situation. If the answer is given after exposure to TMS, treatment may be discontinued or reduced.

The MINI contains a module that asks subjects about suicidal ideation and behavior in the past month. The six items in this module have a possible point total of 33. A score above 6 corresponds to a "Moderate" current risk of suicide, while a score of 10 or above indicates a "High" current suicide risk. In cases where a subject reports a score of 6 or greater, the above procedure will be followed by study personnel.

8.3 Notification, Recording, and Response to Seizure During TMS

Subjects will be given TMS treatment by a trained study nurse or TMS technician under the supervision of the study psychiatrist. In the event of a seizure during the TMS treatment, the modified DHMS seizure protocol will be followed. Treatment will be immediately halted, and the study Neurologist or consult resident will be paged. The seizure will be timed, and the Neurologist on call will determine whether treatment should be continued or if the patient should be withdrawn. A description of the event, including the time of the seizure and the response, as well as study personnel who were notified will be documented in REDcap under **Safety Reporting**.

Additional safety measures may be taken if the subject experiences seizures either during or after the TMS session. As indicated in Procedures, the patient will be accompanied by a proxy in the period between treatment days 1-2 and 2-3. The proxy will be given contact information for the on-call study neurologist, and educated about safety protocol in the event of a seizure. Depending on the participant's response to the TMS, the amount of treatment may be reduced on the subsequent day(s) or terminated altogether. This decision will be made by the study neurologist.

8.4 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period

must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

8.5 Reporting of Serious Adverse Events and Unanticipated Problems

Investigators and the protocol sponsor must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported are those that are:

- related to study participation,
- unexpected, and
- serious or involve risks to subjects or others (see definitions, section 8.1).

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

8.5.1 Investigator reporting: notifying the Dartmouth IRB

This section describes the requirements for safety reporting by investigators who are Dartmouth faculty, affiliated with a Dartmouth research site, or otherwise responsible for safety reporting to the Dartmouth IRB. The Dartmouth College IRB (CPHS) requires expedited reporting of those events related to study participation that are unforeseen and indicate that participants or others are at increased risk of harm. The Dartmouth IRB will not acknowledge safety reports or bulk adverse event submissions that do not meet the criteria outlined below. The Dartmouth IRB requires researchers to submit reports of the following problems within 10 working days from the time the investigator becomes aware of the event:

- Any adverse event (regardless of whether the event is serious or non-serious, on-site or off-site) that occurs any time during or after the research study, which in the opinion of the principal investigator is:

  Unexpected (An event is “unexpected” when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.)

  AND

  Related to the research procedures (An event is “related to the research procedures” if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.)

Reporting Process

Unanticipated problems posing risks to subjects or others as noted above will be reported to the Dartmouth IRB using the form: “Unanticipated Problems Posing Risks to Subjects or Others Including Reportable Adverse Events” or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator’s study file.

Reporting Deaths: more rapid reporting requirements

Concerning deaths that occur during the course of a research study, the following describes the more rapid reporting requirement of the Dartmouth IRB for specific situations:

- Report the event within 24 hours when the death is unforeseen (unexpected) and indicates participants or others are at increased risk of harm.
- Report the event within 72 hours, for all other deaths, regardless of whether the death is related to study participation.

For reportable deaths, the initial submission to the Dartmouth IRB may be made by contacting the IRB Director or Associate Director. The AE/Unanticipated Problem Form is required as a follow up to the initial submission.

Other Reportable events:
For clinical drug trials, the following events are also reportable to the Dartmouth IRB:

- Any adverse experience that, even without detailed analysis, represents a serious unexpected adverse event that is rare in the absence of drug exposure (such as agranulocytosis, hepatic necrosis, Stevens-Johnson syndrome).
- Any adverse event that would cause the sponsor to modify the investigators brochure, protocol or informed consent form, or would prompt other action by the IRB to assure protection of human subjects.
- Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency. For example:
  - An interim analysis indicates that participants have a lower rate of response to treatment than initially expected.
  - Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.
  - A paper is published from another study that shows that an arm of your research study is of no therapeutic value.
- Change in FDA safety labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
- Breach of confidentiality
- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- Protocol violation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the investigator placed one or more participants at increased risk, or affects the rights or welfare of subjects.

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8.6 Unblinding Procedures

All patients will receive stimulation and unblinding will not play a role in this study.

8.7 Stopping Rules

Study safety will be monitored by the co-PIs .The study will be stopped at if the following endpoints are reached:

1. If recruitment for the study in not feasible
   a. no recruitment after 1 year
   b. > 4 drop outs due to any reason (80% feasibility)
2. If TMS is deemed unsafe to patients with epilepsy

a. > 3 patients with increase in baseline seizure frequency
b. > 3 patients with significant worsening of depression
c. > 3 patients with significant side effects of TMS other than seizures

8.8 Medical Monitoring

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

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data and original records will be maintained by the research coordinator at Dartmouth-Hitchcock Medical Center. All source data will be stored in a locked cabinet or office. Demographics and outcome data of participants in the study will be manipulated and stored on a secure, web-based application called REDcap and/or shared drive used for the Department of Neurology's research purposes and managed by the Information Technology Department at Dartmouth-Hitchcock Medical Center. The department follows industry standard procedures for securing the computers, servers, and networks physically and electronically. REDcap will be used as an electronic case report form. Participants will be assigned a random generated number and any identifying information or PHI will be removed prior to analysis.

9.3 Retention

Electronic data will be stored indefinitely. The physical forms and paper data will be kept for three years after completion of the trial.

10 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

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

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

11 Study Finances

11.1 Funding Source

This study is financed through a grant from the Diamond Interdisciplinary Neuroscience Grant.

11.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All Dartmouth investigators will follow the Dartmouth conflict of interest policy.

11.3 Subject Stipends or Payments

The following stipends will be given to study subjects

1. Patient participation stipend - $50 per day of stimulation (3 total) + $50 for final visit
2. Housing stipend up to $330 for 2 night stay
3. Food stipend $20 per day (lunch only) x 3 days

12 References

1. Fisher, R.S., et al., *Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE).* Epilepsia, 2005. **46**(4): p. 470-2.
2. England, M.J., et al., *Epilepsy across the spectrum: promoting health and understanding. A summary of the Institute of Medicine report.* Epilepsy Behav, 2012. **25**(2): p. 266-76.
3. 2014 NINDS Benchmarks for Epilepsy Research. 2014. 2016, a.h.w.n.n.g.r.e.B.-F.-P.p.
4. Fiest, K.M., et al., *Depression in epilepsy: a systematic review and meta-analysis.* Neurology, 2013. **80**(6): p. 590-9.
5. Kobau, R., F. Gilliam, and D.J. Thurman, *Prevalence of self-reported epilepsy or seizure disorder and its associations with self-reported depression and anxiety: results from the 2004 HealthStyles Survey.* Epilepsia, 2006. **47**(11): p. 1915-21.
6. Kanner, A.M., *Depression in epilepsy: prevalence, clinical semiology, pathogenic mechanisms, and treatment.* Biol Psychiatry, 2003. **54**(3): p. 388-98.
7. Akanuma, N., et al., *Psychiatric comorbidity in adult patients with idiopathic generalized epilepsy.* Epilepsy & Behavior, 2008. **13**(1): p. 248-251.
8. Cutting, S., et al., *Adult-onset idiopathic generalized epilepsy: Clinical and behavioral features.* Epilepsia, 2001. **42**(11): p. 1395-1398.
9. Meldolesi, G.N., et al., *Factors associated with generic and disease-specific quality of life in temporal lobe epilepsy.* Epilepsy Res, 2006. **69**(2): p. 135-46.
10. Cramer, J.A., et al., *The impact of comorbid depression on health resource utilization in a community sample of people with epilepsy.* Epilepsy Behav, 2004. **5**(3): p. 337-42.
11. Mendez, M.F., J.L. Cummings, and D.F. Benson, *Depression in epilepsy. Significance and phenomenology.* Arch Neurol, 1986. **43**(8): p. 766-70.

12. Seethalakshmi, R. and E.S. Krishnamoorthy, *Depression in epilepsy: phenomenology, diagnosis and management.* Epileptic Disord, 2007. **9**(1): p. 1-10.
13. Robertson, M.M., M.R. Trimble, and H.R. Townsend, *Phenomenology of depression in epilepsy.* Epilepsia, 1987. **28**(4): p. 364-72.
14. Kanner, A.M. and A. Balabanov, *Depression and epilepsy: how closely related are they?* Neurology, 2002. **58**(8 Suppl 5): p. S27-39.
15. Kanner AM, W.J., Barry J, Hermann B, Meador KJ, Gilliam F. Atypical depressive episodes in epilepsy: a study of their clinical characteristics and impact on quality of life. Neurology. 2004;62(suppl 5):A249.
16. Arnone, D., et al., *Computational meta-analysis of statistical parametric maps in major depression.* Hum Brain Mapp, 2016.
17. Davidson, R.J., D.C. Jackson, and N.H. Kalin, *Emotion, plasticity, context, and regulation: perspectives from affective neuroscience.* Psychol Bull, 2000. **126**(6): p. 890-909.
18. Lorenzetti, V., et al., *Structural brain abnormalities in major depressive disorder: a selective review of recent MRI studies.* J Affect Disord, 2009. **117**(1-2): p. 1-17.
19. Bromfield, E.B., et al., *Cerebral metabolism and depression in patients with complex partial seizures.* Arch Neurol, 1992. **49**(6): p. 617-23.
20. Salzberg, M., et al., *Depression in temporal lobe epilepsy surgery patients: an FDG-PET study.* Epilepsia, 2006. **47**(12): p. 2125-30.
21. Butler, T., et al., *Cortical thickness abnormalities associated with depressive symptoms in temporal lobe epilepsy.* Epilepsy Behav, 2012. **23**(1): p. 64-7.
22. Finegersh, A., et al., *Bilateral hippocampal atrophy in temporal lobe epilepsy: effect of depressive symptoms and febrile seizures.* Epilepsia, 2011. **52**(4): p. 689-97.
23. Salgado, P.C., C.L. Yasuda, and F. Cendes, *Neuroimaging changes in mesial temporal lobe epilepsy are magnified in the presence of depression.* Epilepsy Behav, 2010. **19**(3): p. 422-7.
24. Shamim, S., et al., *Temporal lobe epilepsy, depression, and hippocampal volume.* Epilepsia, 2009. **50**(5): p. 1067-71.
25. Tebartz van Elst, L., et al., *Amygdala enlargement in dysthymia--a volumetric study of patients with temporal lobe epilepsy.* Biol Psychiatry, 1999. **46**(12): p. 1614-23.
26. Arns, M., et al., *EEG alpha asymmetry as a gender-specific predictor of outcome to acute treatment with different antidepressant medications in the randomized iSPOT-D study.* Clin Neurophysiol, 2016. **127**(1): p. 509-19.
27. Allen, J.J., J.A. Coan, and M. Nazarian, *Issues and assumptions on the road from raw signals to metrics of frontal EEG asymmetry in emotion.* Biol Psychol, 2004. **67**(1-2): p. 183-218.
28. Davidson, R.J., K.M. Putnam, and C.L. Larson, *Dysfunction in the neural circuitry of emotion regulation--a possible prelude to violence.* Science, 2000. **289**(5479): p. 591-4.
29. Debener, S., et al., *Is resting anterior EEG alpha asymmetry a trait marker for depression?* Neuropsychobiology, 2000. **41**(1): p. 31-37.
30. Funk, A.P. and M.S. George, *Prefrontal EEG asymmetry as a potential biomarker of antidepressant treatment response with transcranial magnetic stimulation (TMS): a case series.* Clinical Eeg and Neuroscience, 2008. **39**(3): p. 125-130.
31. Gollan, J.K., et al., *Frontal alpha EEG asymmetry before and after behavioral activation treatment for depression.* Biol Psychol, 2014. **99**: p. 198-208.
32. Goodman, R.N., et al., *Stress, emotion regulation and cognitive performance: the predictive contributions of trait and state relative frontal EEG alpha asymmetry.* Int J Psychophysiol, 2013. **87**(2): p. 115-23.
33. Jaworska, N., et al., *alpha Power, alpha asymmetry and anterior cingulate cortex activity in depressed males and females.* J Psychiatr Res, 2012. **46**(11): p. 1483-91.
34. Mathersul, D., et al., *Investigating models of affect: Relationships among EEG alpha asymmetry, depression, and anxiety.* Emotion, 2008. **8**(4): p. 560-572.
35. Colgin, L.L., *Mechanisms and functions of theta rhythms.* Annu Rev Neurosci, 2013. **36**: p. 295-312.
36. Mayberg, H.S., *Limbic-cortical dysregulation: A proposed model of depression.* Journal of Neuropsychiatry and Clinical Neurosciences, 1997. **9**(3): p. 471-481.

37. Broadway, J.M., et al., *Frontal Theta Cordance Predicts 6-Month Antidepressant Response to Subcallosal Cingulate Deep Brain Stimulation for Treatment-Resistant Depression: A Pilot Study.* Neuropsychopharmacology, 2012. **37**(7): p. 1764-1772.
38. Leuchter, A.F., et al., *Resting-State Quantitative Electroencephalography Reveals Increased Neurophysiologic Connectivity in Depression.* Plos One, 2012. **7**(2).
39. 2014., A.C.G.t.T.M.S.N.Y.O.U.P.
40. Gaynes, B.N., et al., *Repetitive Transcranial Magnetic Stimulation for Treatment-Resistant Depression: A Systematic Review and Meta-Analysis.* Journal of Clinical Psychiatry, 2014. **75**(5): p. 477-U196.
41. Rossi, S., et al., *Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research.* Clinical Neurophysiology, 2009. **120**(12): p. 2008-2039.
42. Sun, W., et al., *Low-frequency repetitive transcranial magnetic stimulation for the treatment of refractory partial epilepsy: A controlled clinical study.* Epilepsia, 2012. **53**(10): p. 1782-1789.
43. Chen, J.J., et al., *Left versus right repetitive transcranial magnetic stimulation in treating major depression: A meta-analysis of randomised controlled trials.* Psychiatry Research, 2013. **210**(3): p. 1260-1264.
44. Berlim, M.T., F. Van den Eynde, and Z.J. Daskalakis, *Clinically Meaningful Efficacy and Acceptability of Low-Frequency Repetitive Transcranial Magnetic Stimulation (rTMS) for Treating Primary Major Depression: A Meta-Analysis of Randomized, Double-Blind and Sham-Controlled Trials.* Neuropsychopharmacology, 2013. **38**(4): p. 543-551.
45. Debener, S., et al., *Is resting anterior EEG alpha asymmetry a trait marker for depression? Findings for healthy adults and clinically depressed patients.* Neuropsychobiology, 2000. **41**(1): p. 31-7.
46. Drevets, W.C., *Functional anatomical abnormalities in limbic and prefrontal cortical structures in major depression.* Cognition, Emotion and Autonomic Responses: The Integrative Role of the Prefrontal Cortex and Limbic Structures, 2000. **126**: p. 413-431.
47. Videbech, P., et al., *The Danish PET/depression project: clinical symptoms and cerebral blood flow. A regions-of-interest analysis.* Acta Psychiatrica Scandinavica, 2002. **106**(1): p. 35-44.
48. Walter, H., et al., *Increased left prefrontal activation in patients with unipolar depression: An event-related, parametric, performance-controlled fMRI study.* Journal of Affective Disorders, 2007. **101**(1-3): p. 175-185.
49. Coan, J.A. and J.J.B. Allen, *Frontal EEG asymmetry as a moderator and mediator of emotion.* Biological Psychology, 2004. **67**(1-2): p. 7-49.
50. Levine J, S.N.S.S.A.F.T.E.E.A.N.T.F.D.S.E.I.C.T.C.N.S.
51. Nasreddine ZS, P.N., Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. Journal of the American Geriatrics Society 2005;53:695-9.
52. Watson, D., L.A. Clark, and A. Tellegen, *Development and Validation of Brief Measures of Positive and Negative Affect - the Panas Scales.* Journal of Personality and Social Psychology, 1988. **54**(6): p. 1063-1070.
53. Rush AJ, T.M., Ibrahim HM, et al. The 16-Item quick inventory of depressive symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biological psychiatry 2003;54:573-83.
54. Dodell-Feder, D., et al., *fMRI item analysis in a theory of mind task.* Neuroimage, 2011. **55**(2): p. 705-712.
55. Winterling D, C.T., Salama M, & Gobert J. A self-rating scale for assessing memory loss. Senile dementias: early detection. 1986; 482-487.

13 Attachments

A. Informed Consent Form
B. Study Visit Guide
C. Study Procedures Table
D. TMS Manual
E. Study monitoring plan