PROTOCOL TITLE: Electroconvulsive therapy amplitude titration for improved clinical outcomes in late-life depression

NCT number: NCT04621786

Date of document: 11/19/2020

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Electroconvulsive therapy amplitude titration for improved clinical outcomes in late-life depression

PRINCIPAL INVESTIGATOR:

Chris Abbott, MD, MS
Department of Psychiatry

ADMINISTRATIVE CONTACT:

Kenia Aguilar-Pineda
Department of Psychiatry

VERSION NUMBER:

v.1

DATE:

November 19, 2020

REGULATORY FRAMEWORK:

Please indicate all that apply:

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FUNDING:

The protocol is funded by the National Institutes of Health (NIH).

Sponsor number:

SPO Click ERA record number: FP00008135

CLINICAL TRIALS

Is this a clinical trial per the NIH definition of a Clinical Trial? ☒ Yes ☐ No

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1) Does the study involve human participants? ☒ Yes ☐ No
2) Are the participants prospectively assigned to an intervention? ☒ Yes ☐ No
3) Is the study designed to evaluate the effect of the intervention on the participants? ☒ Yes ☐ No
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If yes to all 4 questions, please confirm that the research team is familiar with and agrees to comply with the investigator requirement to register the study on the ClinicalTrials.gov database. Additionally, the approved consent document(s) must be uploaded to the ClinicalTrials.gov database ☒ Yes ☐ No

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Table of Contents

1. Objectives

Electroconvulsive therapy (ECT) stimulation parameter selection reflects a balance between efficacy and cognitive adverse effects. ECT stimulation parameters associated with more antidepressant efficacy (non-focal electrode placement, longer pulse width) are associated with increased risk of cognitive adverse effects. *Amplitude is currently fixed at 800 or 900 milliamperes (mA) in standard clinical practice with no clinical or scientific basis.* Amplitude determines the intensity of the induced electric field (E-field). With a fixed extracranial amplitude, the ECT "dose" as represented by the E-field is highly variable due to anatomic differences in skin, skull, fluid, and brain tissue. This anatomic variability is prominent in older (age 50+) depressed patients and can compromise both antidepressant efficacy (insufficient stimulation of mood-related circuitry) and safety (inducing cognitive impairment due to excessive stimulation of cognitive related circuitry).

Our long-term goal is focused on advancing treatment for older adults with depressive disorders by refining neuromodulation stimulus parameters to improve efficacy and cognitive safety. Our BRAIN Initiative project (MH111826) used right unilateral electrode placement (RUL) and randomized older ECT subjects to 600, 700, and 800 mA treatment arms. Our results demonstrated a trade-off between antidepressant (improved with higher amplitudes) and cognitive (improved with lower amplitudes) outcomes. Subjects in the 600 mA arm had worse depression outcomes, less neuroplasticity, and cognitive safety, while subjects in the higher amplitude arms (700 and 800 mA) had improved antidepressant outcomes, more neuroplasticity, and cognitive deficits.

Amplitude titration, as proposed here, can reduce the variability related to fixed amplitude dosing and optimize clinical and cognitive outcomes. *The goal of this project is to change standard ECT parameter selection from a fixed amplitude with variable pulse number (combination of pulse train duration and frequency) to an individualized and empirically determined amplitude with fixed pulse number*. To achieve this goal, we will focus on the relationship between amplitude titrated seizure threshold and treatment-responsive changes in hippocampal neuroplasticity with RUL fixed amplitude ECT. Fixed amplitude ECT results in variable E-fields and inconsistent changes in hippocampal neuroplasticity. In contrast, computational and pre-translational investigations have demonstrated that amplitude titration results in consistent E-fields. Seizure titration amplitudes (based on historic data, 233 to 544 mA) are below the amplitude range of FDA-approved ECT devices (500 to 900 mA) and will require an adaptor to reduce the amplitude (FDA Investigational Device Exemption). Amplitude titration will also be below the hippocampal neuroplasticity threshold and insufficient for antidepressant response. The difference between RUL amplitude titration and RUL fixed amplitude (800 mA) ECT will determine the degree of target engagement with the hippocampus. To illustrate, subjects with low amplitude seizure threshold of ~250 mA (800/250, high fixed/titration amplitude ratio) will have significant changes in hippocampal neuroplasticity. Subjects with high amplitude ~500 mA (800/500, low fixed/titration ratio) will have minimal changes in hippocampal neuroplasticity. The relationship between amplitude titration and fixed amplitude hippocampal neuroplasticity will be used to develop the amplitude multiplier required for consistent and clinically effective ECT dosing. Amplitude titration with

multiplier will be associated with the "sweet spot" for hippocampal neuroplasticity: sufficient for antidepressant response but not excessive thus resulting in cognitive safety.

Older depressed subjects (n = 40) will first receive RUL amplitude titration (first treatment) and then RUL fixed amplitude (800 mA) and fixed pulse number ECT (subsequent treatments). We will 1) verify results from pre-translational investigations that demonstrated the relationship between current pulse amplitude and a whole brain E-field metric (I/E_{brain}), and 2) determine the relationship between current pulse amplitude and treatment-responsive changes in hippocampal neuroplasticity from RUL fixed-amplitude (800 mA) ECT.

H1: Amplitude seizure titration will have a positive correlation with I/E_{brain}.

H2, Go/No-Go criterion: The ratio of amplitude titrated seizure threshold to fixed amplitude ECT will demonstrate a linear relationship with treatment-responsive changes in hippocampal neuroplasticity. This relationship will determine the "neuroplasticity multiplier" to bridge from amplitude titration to hippocampal neuroplasticity.

2. Background

Electroconvulsive therapy (ECT) stimulation parameter selection reflects a balance between efficacy and cognitive adverse effects. ECT stimulation parameters associated with more antidepressant efficacy (non-focal electrode placement, longer pulse width) are associated with increased risk of cognitive adverse effects. Amplitude is currently fixed at 800 or 900 milliamperes (mA) in standard clinical practice with no clinical or scientific basis. Amplitude determines the intensity of the spatial distribution of the electric field (E-field). With a fixed extracranial amplitude, the ECT "dose" as represented by the E-field is highly variable due to anatomic differences in skin, skull, fluid, and brain tissue. This anatomic variability is prominent in older (age 50+) depressed patients and can compromise both antidepressant efficacy (insufficient stimulation of mood-related circuitry) and safety (inducing cognitive impairment due to excessive stimulation of cognitive related circuitry). Amplitude titration, as proposed in this current proposal, can reduce the variability related to fixed amplitude dosing and optimize clinical and cognitive outcomes. The goal of this project is to change standard ECT parameter selection from a fixed amplitude to an individualized and empirically determined amplitude. To achieve this goal, we will focus on the relationship between amplitude titration and treatment-responsive changes in hippocampal neuroplasticity with RUL fixed amplitude ECT. Fixed amplitude ECT results in variable E-field or ECT dose. Over the course of an ECT series, the variable ECT dose will result in inconsistent changes in hippocampal neuroplasticity. In contrast, pre-translational investigations have demonstrated that amplitude titration results in a consistent E-field or ECT "dose". Seizure titration amplitudes (based on historic data, 233 to 544 mA) are below the amplitude range of FDA-approved ECT devices (500 to 900 mA) and will require an adaptor to reduce the output amplitude (Investigational Device Exemption). Amplitude titration will also be below the hippocampal neuroplasticity threshold and insufficient for antidepressant response. The difference between RUL amplitude titration and RUL fixed amplitude (800 mA) ECT will determine

the degree of target engagement with the hippocampus. To illustrate, subjects with low amplitude titration of ~250 mA (800/250, high fixed/titration amplitude ratio) will have significant changes in hippocampal neuroplasticity. Subjects with high amplitude titration ~500 mA (800/500, low fixed/titration ratio) will have minimal changes in hippocampal neuroplasticity. The relationship between amplitude titration and fixed amplitude hippocampal neuroplasticity will be used to develop the amplitude multiplier required for consistent and clinically effective ECT dosing. A randomized controlled trial will then compare hippocampal neuroplasticity, antidepressant, and cognitive outcomes between amplitude titration with neuroplasticity multiplier (fixed pulse number) and traditional fixed amplitude ECT (800 mA, variable pulse number) in older depressed subjects.

3. Study Design

Subjects will receive their baseline imaging, clinical, and neuropsychological assessment 24 to 48 hours prior to the first ECT session (V1). Subjects will first receive RUL amplitude titration (first treatment) and then RUL fixed amplitude (800 mA) and fixed pulse number ECT (subsequent treatments). We will 1) verify results from pre-translational investigations that demonstrated the relationship between current pulse amplitude and a whole brain E-field metric (I/E_{brain}), and 2) determine the relationship between current pulse amplitude and treatment-responsive changes in hippocampal neuroplasticity from RUL fixed-amplitude (800 mA) ECT. Treatments will continue thrice weekly until clinical response, which typically occurs between six and twelve treatments [14]. Subjects will receive their second assessment (V2) one day after the sixth ECT treatment and the final assessment (V3) one day after the ECT series. Subjects who do not demonstrate improvement by the V2 assessment (< 25% reduction from baseline IDS-C_{30} total score) will transition to traditional BT for the remainder of the ECT series. The anesthesiologist will determine the appropriate dose of methohexital (general anesthetic) and succinylcholine (depolarizing neuromuscular blocker). Anesthetic medications, electroencephalographic seizure duration, motor seizure duration, and maximum ictal heart rate will be recorded for each treatment.

Subjects (n = 40) will receive amplitude titrated seizure threshold during the first treatment with RUL [105]. The Soterix 4X1 High Definition ECT Multi-channel Stimulation Interface ("Soterix Interface") is a passive amplitude reducer for the MECTA 5000Q. The Soterix Interface reduces the amplitude range to 200 mA and permits 50 mA incremental dosing throughout the 200 to 900 mA dosing range. Pulse width (1.0 ms), pulse train duration (8 s), and frequency (20 Hz, 320 pulses) will be fixed for amplitude titration. Subjects will receive stimulations starting with 200 mA with 50 mA increases until seizure activity is initiated. Clinical judgement will define seizure adequacy based on duration and morphology. In addition, subjects will receive amplitude titrated motor threshold after administration of general anesthesia during the second ECT treatment (exploratory aim, see "Motor Titration" below). After amplitude titrated seizure threshold, subsequent treatments will be completed with RUL fixed 800 mA with the same pulse width (1.0 ms) and pulse number (8 s, 20 Hz, and 320 pulses). If the subject fails to demonstrate improvement at V2 (< 25% reduction from baseline IDS-C_{30} total score), the subject will then receive traditional BT for the remainder of the ECT series.

4. Inclusion and Exclusion Criteria

Entry criteria will include men and women of all backgrounds.

Inclusion criteria: 1) Structured Clinical Interview for DSM-5 (SCID-5) will confirm diagnosis of major depressive disorder (MDD; with or without psychotic features); 2) clinical indications for ECT with right unilateral electrode placement including treatment resistance or a need for a rapid and definitive response, 3) right-handedness, 4) age range between 50 and 80 years, and 5) English-speaking (many of the neuropsychological tests are only available in English). Antidepressant medications will be continued as clinically indicated. To maintain feasibility and retention, as needed medications will be permitted for anxiety (lorazepam, total dose 2mg/day) and insomnia (trazodone, total dose: 150mg/day). Late-life depression is often associated with cognitive impairment. Cognitive impaired older adults will be included in the study sample.

Exclusion criteria*:* 1) Defined neurological or neurodegenerative disorder (e.g., traumatic brain injury, epilepsy, Alzheimer's disease); 2) other psychiatric conditions (e.g., schizophrenia, bipolar disorder); 3) current drug or alcohol use disorder (except for nicotine); 4) contraindications to MRI; 5) prisoners; and 6) pregnancy (pre-menopausal participants will receive pregnancy test, which is clinically indicated for ECT and not part of study protocol).

5. Number of Subjects

We will recruit 40 subjects who meet inclusion criteria.

6. Study Timelines

Our total sample size (n = 40) allows for a conservative 20% attrition rate leaving a final sample size of 32. This recruitment rate of 20 subjects per year will complete subject recruitment 2 years after study initiation. We have a successful recruitment and retention history for ECT-imaging investigations of approximately 20 subjects per year with this demographic for the last decade and are well poised to meet the recruitment/enrollment goals delineated in this project proposal.

7. Study Endpoints

After recruiting a minimum of 32 subjects, we will assess the following relationships: 1) amplitude-determined seizure threshold and whole brain conductivity metrics (I/E_{brain}); and 2) amplitude titration and changes in right hippocampal volume with 800 mA ECT.

8. Research Setting

All data collection will take place at the UNM Center for Psychiatric Research, the Mind Research Network or the ECT service at the University of New Mexico. All clinical

assessments and neuropsychological testing will be conducted in an interview room. These rooms are scheduled by research staff. The MRI scanner is located at the Mind Research Network. The optional EEG monitoring will be conducted at the ECT clinical services: the UNMH Post Anesthesia Care Unit (inpatient) or UNM Outpatient Surgical Imaging Services (outpatient).

9. Resources Available

Investigators:

- The PI (Dr. Abbott) has recently completed a NIH U01 BRAIN Initiative project (MH111826) focused on ECT amplitude and medial temporal lobe engagement that provided the preliminary data for this protocol. Dr. Abbott has received extramural funding focused on ECT-neuroimaging investigations since 2012. He is the UNM Neuromodulation Division Chief, Medical Director of the UNM ECT Service, and a member of the Global ECT MRI Research Collaboration (GEMRIC) steering committee. He has completed career training awards focused on neuroimaging biomarkers associated with late-life depression and has numerous peer-reviewed publications on neuroimaging correlates of ECT response. ECT, clinical and cognitive assessments and neuroimaging data acquisition will be conducted at the UNM/Mind Research Network in Albuquerque, New Mexico.
- Dr. Davin Quinn (UNM), Medical Director of the UNM Consultation Liaison Service, has an extramural funding focused on neurostimulation in neuropsychiatric disorders, including late-life depression. He is the UNM Psychosomatics Division Chief, Medical Director of the UNM TMS Service, and the UNM Chief of Staff. He has worked with Dr. Abbott on the UNM ECT service for the last ten years and will assist with subject recruitment and assessments.
- Dr. Erik Erhardt (Co-I, UNM) has expertise in neuroimaging and statistical expertise. He has been a key collaborator with past and current investigations with study design, statistical analysis, and result interpretation.

Figure 2. Soterix 4X1 High Definition ECT Multi-channel Stimulation Interface

Soterix High Definition ECT Multi-channel Stimulation Interface (information from Soterix Operator's Manual): The Soterix 4X1 HD-ECT Multi-Channel Stimulation Interface ("Soterix Interface") is an accessory to a 2-channel ECT stimulator and does not function as a stand-alone electrical stimulator or generator. The Soterix Interface is designed to be used as an interface device and the stimulation leads. The device is designed to be operated in either SCAN or PASS modes. The SCAN mode is used to determine lead quality values prior to switching to the PASS mode. The PASS mode provides the option for attenuating ECT device output. When the attenuation feature is enabled, the PASS mode only attenuates the stimulus current amplitude leaving other

treatment parameters unchanged (pulse width, frequency and pulse train duration). The attenuated current range is between 200 – 500 mA with 2 mA increments (50 mA dose increments will be used in this proposal). The Patient Stimulus cable (output cable of the ECT device) is used to connect the device to the Soterix Interface, which will then connect to right unilateral stimulation electrodes (traditional stimulation handles with 5 cm spherical diameter). The Research Strategy delineates how the Soterix Interface will be used in this project. We have received FDA Investigational Device Exemption approval to use the Soterix Interface for this investigation.

MRI: Siemens 3T Trio with Total Imaging Matrix (TIM) Application Suite (Mind Research Network): The Trio 32-channel system represents state of the art in MRI hardware. It is capable of BOLD EPI, diffusion tensor imaging, perfusion and diffusion imaging, and spectroscopy. With 32 usable receiver channels as standard, the system allows for the use of current phased array coils (from 4 to 16) to improve sensitivity and speed of acquisition and is ready for future coil designs with more than 16 elements. This system is interfaced to an MR-compatible patient monitoring. The MRI is non-contrast.

10. Prior Approvals

Departmental Review Form signed by Department Chair is uploaded into Click under "supporting documents." Investigational Device Exemption approval from the Food and Drug Administration for the Soterix Interface was received on July 10, 2020 (see "supporting documents"). Additionally, we have obtained a letter of support from Dr. Abhishek Datta, Scientist and Chief Technology Officer of Soterix Medical.

11. Multi-Site Research

N/A

12. Study Procedures

Study Protocol: Subjects will receive their baseline imaging, clinical, and neuropsychological assessment 24 to 48 hours prior to the first ECT session (V1). Treatments will continue thrice weekly until clinical response, which typically occurs between six and twelve treatments [14]. Subjects will receive their second assessment (V2) one day after the sixth ECT treatment and the final assessment (V3) one day after the ECT series. Subjects who do not demonstrate improvement by the V2 assessment (< 25% reduction from baseline IDS-C_{30} total score) will transition to traditional BT for the remainder of the ECT series. The anesthesiologist will determine the appropriate dose of methohexital (general anesthetic) and succinylcholine (depolarizing neuromuscular blocker). Anesthetic medications, electroencephalographic seizure duration, motor seizure duration, and maximum ictal heart rate will be recorded for each treatment.

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Interface reduces the amplitude range to 200 mA and permits 50 mA incremental dosing throughout the 200 to 900 mA dosing range. Pulse width (1.0 ms), pulse train duration (8 s) frequency (20 Hz, 320 pulses) and will be fixed for amplitude titration. Subjects will receive stimulations starting with 200 mA with 50 mA increases until seizure activity is initiated. Clinical judgement will define seizure adequacy based on duration and morphology. In addition, subjects will receive amplitude titrated motor threshold after administration of general anesthesia during the second ECT treatment (exploratory aim, see "Motor Titration" below). After amplitude titrated seizure threshold, subsequent treatments will be completed with RUL fixed 800 mA (traditional amplitude) with the same pulse width (1.0 ms) and pulse number (8 s, 20 Hz, and 320 pulses). If the subject fails to demonstrate improvement at V2 (< 25% reduction from baseline IDS-C_{30} total score), the subject will then receive traditional bitemporal electrode placement for the remainder of the ECT series.

Clinical Assessments: The clinician-rated 30-item Inventory of Depressive Symptomatology (IDS-C_{30}) will be the primary depression severity measure [83]. The number of subjects transitioning to bitemporal electrode placement after the mid-ECT assessment (V2, see Study Protocol) will be the secondary depression outcome. The IDS-C_{30} includes depressive items in accordance with the DSM-5. Each item is scored from 0 - 3 and summed for a total score between 0 – 84. The initial visit (V1) will also include the Maudsley Staging Method to measure antidepressant treatment resistance within the current depressive episode [84], ECT Appropriateness Scale to assess the indication for ECT [85], Medical History form to gauge overall medical burden, Framingham Stroke Risk Profile to measure vascular burden [86], and Edinburgh Handedness Inventory to define handedness [87]. Additional characteristics of the current and past depressive episodes will also be recorded during the initial visit: age of onset, age of first treatment, number of depressive episodes, and depressive episode duration.
Rationale: The IDS-C_{30} has excellent psychometric properties [88], includes symptoms relevant to depression subtypes (melancholic and atypical), and converts to other depression rating scales relevant to NIH data sharing.

Neuropsychological Assessments: The Delis Kaplan Executive Function System (DKEFS) Verbal Fluency test will be the primary cognitive measure [89]. The Montreal Cognitive Assessment (MOCA), a measure of global cognitive function that is sensitive to gross neurocognitive abnormalities, will screen for preexisting cognitive impairment [90,91]. The Test of Premorbid Function (TOPF) will estimate premorbid intellectual function for use as a covariate in cognitive analyses [92]. The Dot Counting Test will measure performance validity [93]. The Autobiographical Memory Test will assess multiple aspects (free recall, retrieval pattern, cognitive efficiency) of retrospective autobiographical memory [94-96]. The Hopkins Verbal Learning Test-Revised (HVLT-R) will measure verbal learning and memory [97,98]. To minimize practice effects, each time point will use a different published HVLT-R version [99]. The DKEFS Color-Word Interference test will measure processing speed, inhibition, initiation, and cognitive flexibility [89,100-103]. The DKEFS Verbal Fluency test will measure phonemic and semantic fluency, and cognitive flexibility. The DKEFS Tower Test will measure planning and problem solving [89]. Lastly, the NIH Toolbox Flanker Inhibitory Control and Attention Test will measure attention and inhibition [104].

Neuroimaging Acquisition and Data Processing

Imaging data will be collected on a 3-Tesla Siemens PRISMA scanner with strong gradients and minimal shading artifact and a 32-channel coil using multiband sequences at the Mind Research Network (MRN). The imaging acquisitions relevant to this project include the following:

1. sMRI (T1): Repetition time (TR) = 2530 milliseconds (ms), echo time (TE) = 1.64, 3.5, 5.36, 7.22, 9.08 ms, Inversion time (TI) = 1200 ms, flip angle = 7.0 °, slices = 192, field of view = 256, matrix 256 × 256, voxel size = 1.0 × 1.0 × 1.0 millimeter (mm) and total acquisition time 6:03 (minutes: seconds).
2. sMRI (T2): TR = 2530 ms, TE = 474 ms, flip angle = 120.0 °, slices = 192, field of view = 256, matrix 256 × 256, voxel size = 1.0 × 1.0 × 1.0 mm and total acquisition time = 5:09.
3. High-resolution T2: TR = 8020 ms, TE = 80 ms, flip angle = 150.0 °, slices = 30, field of view = 150, matrix 384 × 384, voxel size = 0.4 × 0.4 × 0.2 mm and total acquisition time = 7:05.

Preprocessing steps with each imaging modality include the following:

1. FreeSurfer Segmentation (T1 and T2): FreeSurfer 6.0 is a set of software tools that utilize the T1 and T2 weighted scans to study the cortical and subcortical anatomy. In the cortical surface stream, the tools construct models of the boundary between white matter and cortical gray matter as well as the pial surface. Once these surfaces are known, an array of anatomical measures becomes possible, including subcortical volumes, cortical thickness, surface area, curvature, and surface normal at each point on the cortex.
2. Medial Temporal Lobe Segmentation (High resolution T2): The Automatic Segmentation of Hippocampal Subfields (ASHS) uses T1- and high-resolution T2-weighted MRI to segment and label hippocampal subfields and medial temporal lobe cortices. The automatic labeling technique uses multi-atlas segmentation and similarity-weighted voting with a learning-based correction [110,111]. An unbiased deformation-based morphometry pipeline will then estimate longitudinal changes in hippocampal subfields [112]. Deformable image registration with a cross-correlation similarity metric generates a point-by-point correspondence map between images at two time points (baseline and follow-up). To avoid bias, registration is performed in a "half-way" space, and equal amounts of deformation and interpolation are applied to the baseline and follow-up images. A mesh representation of the ASHS segmentation of the medial temporal lobe substructures in the baseline image is used to measure change in volume between baseline and follow-up.
3. Electric Field Modeling: Our research team has extensive experience with t E-field modeling approaches. The Realistic vOlumetric Approach to Simulate Transcranial Electric Stimulation (ROAST) and Simulation of Non-Invasive Brain Stimulation (SimNIBS) were both used for our preliminary data [30,31]. Here, we describe the SimNIBS methods, which informed our power analyses. SimNIBS creates subject specific, anatomically realistic volume conductor model. The T1 and T2-weighted scans are segmented into skin, bone, eyes, cerebral spinal fluid, ventricles, and grey and white matter with a combination of FMRIB Software Library (FSL) [113] and

Statistical Parametric Mapping 12 (SPM12) Computational Anatomy Toolbox [114,115]. SimNIBS then turns this segmentation into a tetrahedral head mesh using GMSH, a three-dimensional finite element (FE) mesh generator, with unique conductivity values for each tissue type. Electrodes are added to the head mesh in either RUL or BT orientation and simulated with corresponding current. SimNIBS then uses a FE solver to calculate the voltages and electric fields corresponding to the stimulation throughout the head mesh.

FDA Investigational Device Exemption: Investigational Device Exemption approval from the Food and Drug Administration for the Soterix Interface was received on July 10, 2020. Additionally, we have obtained a letter of support from Dr. Abhishek Datta, Scientist and Chief Technology Officer of Soterix Medical. We have a successful recruitment and retention history for ECT-imaging investigations of approximately 20 subjects per year with this demographic for the last decade and are well poised to meet the recruitment/enrollment goals delineated in this project proposal. Future investigations will focus on the optimal strength of hippocampal volumetric increases to further clarify the "sweet spot" of antidepressant response in conjunction with cognitive safety.

13.Data Analysis

Preliminary Data: Amplitude titration has been completed with non-human primates but has yet to be completed with human subjects and modern ECT parameters. *I/E_{brain} bridges the gap from amplitude titration in non-human primates to changes in hippocampal neuroplasticity in human subjects.* I/E_{brain} is the ratio of electrode current strength (I) to the E-field strength in the brain (E_{brain}) [21]. E_{brain} will be computed as the 90th percentile of E-field magnitudes from all voxels in the brain, serving as an estimate of the peak induced field strength while avoiding the influence of tissue boundary effects that could bias the absolute maximum E-field values. For example, one subject with 800 mA extracranial amplitude produces 0.8 V/cm 90th percentile E-field strength. The ratio would be 1000 mA/V/cm, which means 1000 mA produces 1 V/cm. A second subject with the same 800 mA extracranial amplitude produces 1.2 V/cm 90th percentile E-field. The ratio would be 667 mA/V/cm, which means 667 mA produces 1 V/cm. E_{brain} is a whole brain E-field metric as the location of seizure duration is unknown.

The relationship from amplitude titration to hippocampal neuroplasticity is illustrated here (**Figure 4**). First, we demonstrate that amplitude-titrated seizure threshold increases with I/E_{brain} in non-human primates (**4A**). Second, we demonstrate that increased I/E_{brain} is related to decreased hippocampal E-field (current dependent metric, input current set here at 1 mA) (**4B1**). For fixed amplitude ECT, I/E_{brain} is inversely related to hippocampal volume change. E_{hippo} is the 95th percentile E-field in the hippocampus and will be an exploratory measure of this investigation. However, the focus on amplitude titrated seizure threshold requires E_{brain}, a whole brain E-field metric, as the regions involved in seizure induction are unknown. Third, we demonstrate that increased hippocampal E-field is related to increased hippocampal neuroplasticity across all amplitudes (600, 700, and 800 mA) and electrode placements (RUL and BT) (**4B2**). This relationship is a replication of the GEMRIC data (Figure 2) with our U01 data. Fourth, we

performed an analysis of a subset of our data comparing I/E_{brain} with hippocampal volumetric change with 800 mA subjects (**4B3**).

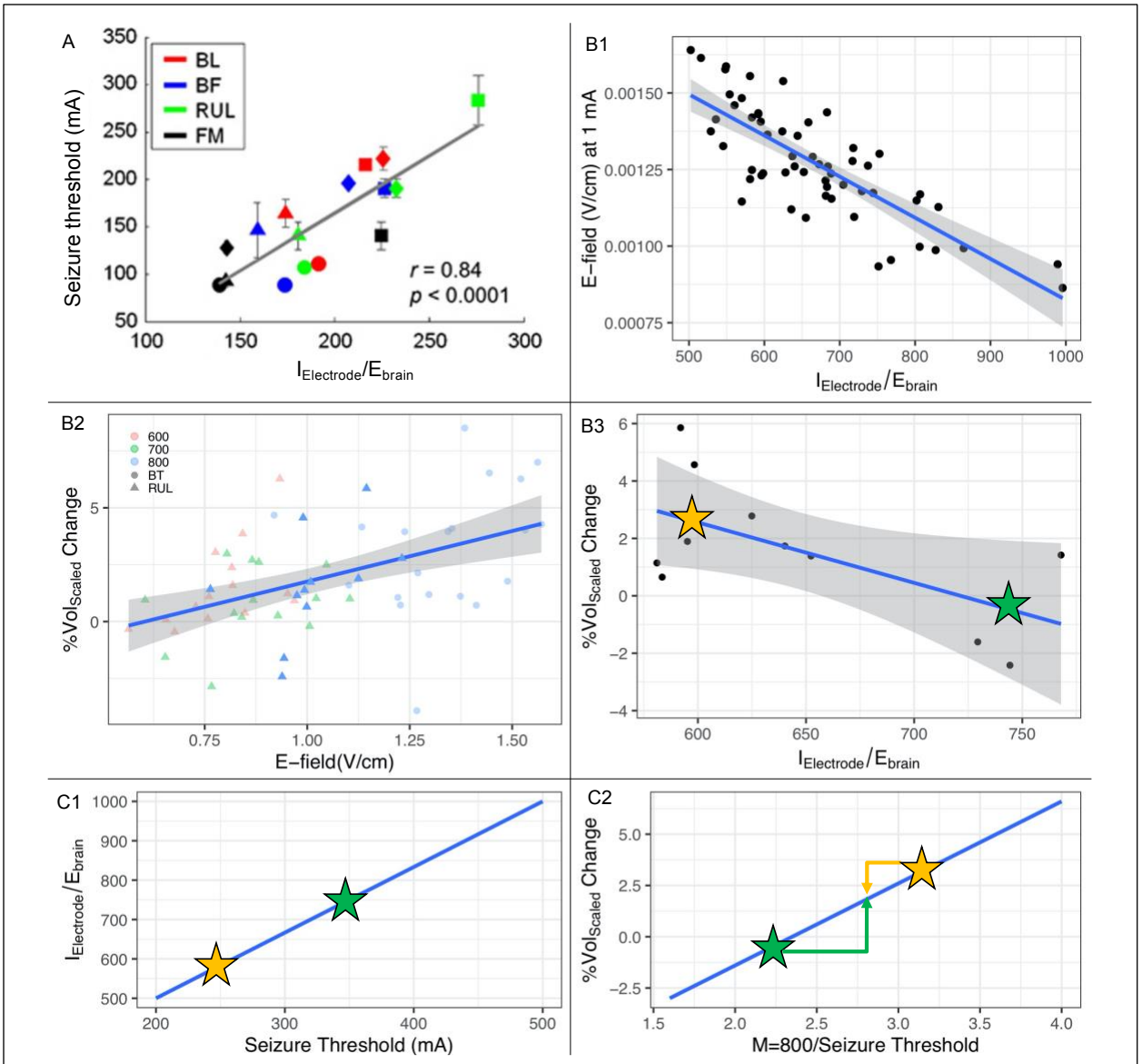

Figure 4: The multi-step relationship from amplitude titration to hippocampal neuroplasticity.
A) Non-human primate data. $I_{electrode}/E_{brain}$ (see description in Preliminary Data). Increased I/E_{brain} is related to increased amplitude required for seizure titration ($r = 0.84$, $p < 0.0001$).
B1) U01 data, all subjects. $I_{electrode}/E_{brain}$ is inversely related to hippocampal E-field magnitude with an amplitude intensity of 1 mA, which is baseline for E-field modeling ($r = -0.79$, Cohen's $f^2 = 1.66$).
B2) U01 data, all subjects. Electrode placement (RUL and BT) and amplitude (600, 700, 800 mA) are based on the subject's last treatment. Right hippocampal E-field magnitude is directly related to right hippocampal neuroplasticity for all amplitude strengths (600, 700, and 800 mA) and electrode placements (right unilateral and bitemporal) ($r = 0.49$, Cohen's $f^2 = 0.33$).
B3) U01 data, subjects from the 800 mA arm. $I_{electrode}/E_{brain}$ is inversely related to right hippocampal neuroplasticity for 800 mA subjects ($r = -0.62$, Cohen's $f^2 = 0.62$).
C1) Hypothesized relationship. Increased $I_{electrode}/E_{brain}$ is related to increased amplitude required for seizure titration (verification of non-human primate data depicted in 4A).
C2) Hypothesized relationship (Go-No-go). The ratio of fixed amplitude ECT (800 mA) relative to amplitude seizure titration will be associated with right hippocampal neuroplasticity.

Summary, interpretation, and alternatives: To illustrate the application of these principles, we use our preliminary data (**4B3**) and hypothesized relationships (**4C1** and **4C2**). We also use the example of 2% hippocampal growth as optimal for antidepressant response (optimal hippocampal growth will be determined with a receiver operating curve (ROC) curve predicting Inventory of Depressive Symptomatology (IDS-C_{30}) total score decrease during the R61). With traditional 800 mA amplitude, the 2% volume increase is related to an I/E_{brain} of ~ 625 mA/V/cm (**4B3**) and fixed/amplitude ratio of ~ 2.7 (**4C2**). Subject #1 (orange star) has a low (250 mA) seizure threshold (ST) (**4C1**), I/E_{brain} of ~ 600 mA/V/cm (**4C2**) and a fixed/amplitude ratio of 800/250 = 3.2 (**4C2**). Subject #1 will need an input current of $2.7 \times ST = 2.7 \times 250\, mA = 675\, mA$ for 2% hippocampal volume increase. In contrast, Subject #2 (green star) has a high (350 mA) seizure threshold, I/E_{brain} of ~ 750 mA/V/cm and a fixed/amplitude ratio of 800/350 = 2.3. In order to achieve the 2% volumetric increase, Subject #2 will require an increased X/amplitude ratio from 2.3 to 2.7. Subject #2 will need an input current of $2.7 \times ST = 2.7 \times 350\, mA = 950\, mA$ for 2% hippocampal volume increase. We stress that the fixed/amplitude ratio ~ 2.7 for 2% hippocampal volume increase is conceptual and will be determined during the R61.

H1: Amplitude seizure titration will have a positive correlation with I/E_{brain} (**Figure 4C1**). This is a replication of the data from the non-human primate data. The relationship between I/E_{brain} and amplitude titration is the foundation for the rationale of this proposal.

Statistical approach for H1: Let $(x, y)_i$ be the observed vector of response for I/E_{brain} and seizure threshold for each patient, $I = 1, \ldots, n$. The Pearson correlation will be calculated and the standard one-sided t-test with 2 degrees-of-freedom will be conducted for testing whether the correlation is positive, H_0: $\rho > 0$.

Power calculation for H1: The observed correlation in Figure 4A is $r = 0.84$ for non-human primates and we expect that the more conservative Cohen's "large" effect size $r = 0.5$ is a realistic lower bound for our population, thus a sample size of n = 29 provides 80% power at a 0.05 / 2 = 0.025 significance level.

Go/No-Go criterion (H2): The ratio of amplitude titration to fixed amplitude ECT will demonstrate a linear relationship with treatment-responsive changes in hippocampal neuroplasticity. This relationship will determine the "neuroplasticity multiplier" to bridge from amplitude titration to hippocampal neuroplasticity.

Statistical approach for H2: We will perform a multiple regression accounting for covariates age and sex, $\%Vol_{Scaled}$ Change = $\beta_0 + \beta_1$ M + β_2 age + β_3 sex, where the effect size is $f2 = R^2 / (1 - R^2)$, with R^2 the coefficient of determination with the interpretation of "the proportion of variance explained" in the response by the model over the grand mean. We will test whether the regression model explains a significant proportion of variance in the response, expecting that the key relationship is between $\%Vol_{Scaled}$ change and multiplier M.

Power calculation for H2: The relationship we are expecting in Figure 4C2 is derived from Figures 4B3 and 4C1. Starting with Figure 4B3, the relationship of I/Ebrain on $\%Vol_{Scaled}$ change has a correlation of $r = -0.62$ with an effect size f2 = 0.624, well above the Cohen's "large" effect size of f2 = 0.35. Figure 4C1 is Figure A with the axes reversed, thus the

correlation is $r = 0.84$. We will assume that the relationship between $\%Vol_{Scaled}$ Change and multiplier M will remain consistent with Cohen's "large" effect size. Then a sample size of n = 36 provides 80% power at a 0.05 significance level.

The Holm Procedure, a multi-step step-down procedure useful for endpoints with any degree of correlation, will adjust the two hypotheses below for multiple comparison [37]. For our situation, this means H1 is tested at the 0.05 / 2 significance level and H2 is tested at 0.05 / (2−1) = 0.05; however, H2 is tested only if H1 is significant.

The Go/No-Go criterion is set to "Go" if we can reject the null hypothesis that H_0: $\beta_1=0$ at a 0.05 significance level in the model specified in Hypothesis H2, that is, that multiplier M remains a significant predictor of $\%Vol_{Scaled}$ Change after adjusting for age and sex.

14. Provisions to Monitor the Data to Ensure the Safety of Subjects

Data safety and monitoring will be carried out to ensure and maintain the scientific integrity of this project and to protect the safety of our participants. Safety monitoring is the process during the study that involves review of accumulated outcome data for groups of subjects to determine if any of the procedures practiced should be altered or stopped. Ultimately, the PI (Abbott) will be responsible for monitoring the safety of the study and complying with the reporting requirements. An independent Data Safety and Monitoring Board (DSMB) will review the study data on a biennial basis with the PI to ensure participant safety (re: subject recruitment at 20 subjects/year, DSMB meetings every ~ 10 participants). The Data Safety and Monitoring Board will include Dr. Sarah Pirio Richardson (DSMB Chair/Dept. of Neurology), Dr. Kathleen Reyes (Dept. of Anesthesiology), and Dr. Eric Clause (PI at Mind Research Network). The board members have no conflicts of interest or roles with the current project. Drs. Pirio Richardson and Claus have experience participating in ECT-related DSMB, and Dr. Reyes has extensive clinical experience with ECT. Continuous, close monitoring of participant safety will include prompt and frequent reporting of safety data (i.e., adverse/serious adverse events) to the DMSB, the University of New Mexico Health Sciences Center Institutional Review Board (UNMHSC IRB) and/or appropriate NIH staff with oversight responsibility. The focus of adverse event reporting will be the first treatment of the ECT series, which is the only experimental treatment for this phase of the project. The first treatment will be amplitude titration (as opposed to the more traditional titration based on pulse number or frequency). The amplitude titration will result in reduced amplitudes (hypothesized range will be between 250 and 550mA, traditional ECT is conducted at 800mA). Adverse events may include expected side effects related to ECT: headaches, nausea (from anesthesia), and muscle aches (from anesthesia). Unexpected side effects (to be determined) will also be reviewed with the DSMB. In addition, relevant published data related to the study protocol will also be presented to the DSMB. The DSMB will evaluate the adverse effects of the first treatment in relation to the expected side effects related to a traditional ECT series. The PI will provide a summary of the safe conduct of the study to NIH and FDA on an annual basis as part of the progress report. All AEs occurring during the course of the study will be collected, documented, and reported to the UNMHSC IRB. The review of data may result in early termination of the study, amendment to the protocol, or changes to

the data collection plan or study forms if it appears that there are adverse events directly related to the first (experimental) treatment. Significant adverse events directly related to the experimental treatment (amplitude titration, treatment#1) such as hospitalization and death will warrant suspension or termination of research. Should the protocol, data collection plans or study forms be amended as a result of data review, the IRB will be notified and the amendment approved prior to study amendment implementation. In addition, the participants will be notified of any significant new findings that develop during the course of research that may affect their wish to continue participation in the study.

15. Withdrawal of Subjects

If at any time a participant decides to withdraw from the study, the participant will be debriefed by the study coordinator or principal investigator as to the reason for their withdrawal. The participant will then be thanked for their time and compensated for the extent of their participation. If the participant wishes to withdraw, they will be asked if they will allow data already collected on them to be used in the study analysis. If not, the data associated to their identifying code will be purged from the study database. A participant could be excluded and withdrawn from the research study in the event that a pre-determined condition exists, including a defined neurological or neurodegenerative disorder (e.g., traumatic brain injury, epilepsy, Alzheimer's disease), other psychiatric conditions (e.g., schizophrenia, bipolar disorder), current drug or alcohol use disorder (except for nicotine), and/or contraindications to MRI.

16. Data Management/Confidentiality

Every effort will be made to protect the confidentiality of participants' records. However, complete confidentiality of records cannot be guaranteed as records may be examined by authorized personnel from the UNM Human Research and Review Committee. Participants will be informed of this possibility prior to signing the consent forms. Otherwise, records will be kept strictly confidential and will not be inspected by any other agency unless required by law. Behavioral and computerized data from the MRI scanning sessions will not contain participants' names or any other identifying information per HIPAA requirements. Data will be de-identified as appropriate to the UNM Human Research and Review Committee and HIPPA requirements by assigning a randomized eight-digit number to each participant upon entry into the study. This number will be used for all correspondence between study investigators and all data collection and analysis after the initial screening visit. MRN has a state-of-the art IT network with all necessary security mechanisms in place. Any personal information entered into computers is password protected and monitored for suspicious activity. In order to contact subjects for telephone visits and/or other matters, it will be necessary to retain names and telephone numbers of active subjects. However, these direct identifiers will not be stored with any clinical data or subject information in order to protect confidentiality. Any direct identifiers will be stored in locked cabinets, on a secure MRN server, and/or the COINS database on a secure HIPAA compliant cloud based server, separate from any clinical data. These will only be accessible by key study personnel. A link between study code numbers and direct

identifiers will be retained in order to contact subjects for visit appointments or at a later date to inform them of newly received information. This link will be retained for the duration of the study. Subjects will be identified only by unique Patient ID numbers in Case Report Forms (CRFs) and electronic CRFs. The CRFs will be maintained in a locked cabinet housed in the Center for Psychiatric Research. These documents will only be accessible by authorized study staff and will comply with HIPPA requirements for the storage of health information. Moreover, all information will be in double-locked rooms per HIPAA specifications. At the time of study closure, all participant identifiers (name, address, etc.) will be made inaccessible to the research team. MRN retains the link between identifiers and URSI indefinitely for the potential future benefit to the research participant. Specifically, it may become medically advantageous in the future for a former participant to have access to the clinical information that may be present in radiological scans and reviews. The results of this research may be presented at meetings or in publications; however, participants' identity will not be disclosed. The participant will be provided with a copy of the consent form to take home.

17.Data and Specimen Banking

Data will be stored in locked cabinets at the UNM Center for Psychiatric Research. Subjects' charts will be stored without direct identifiers. Only research staff designated by Dr. Abbott will have access to these records. Other than the research team, the study sponsor and the HRRC will be permitted access to the records. In order to contact subjects for telephone visits and/or other matters, it will be necessary to retain names and telephone numbers of active subjects. However, these direct identifiers will not be stored with any clinical data or subject information in order to protect confidentiality. Any direct identifiers will be stored in locked cabinets and on a secure MRN server, and/or the COINS database on a secure HIPAA compliant cloud based server, separate from any clinical data. These will only be accessible by key study personnel. A link between study code numbers and direct identifiers will be retained in order to contact subjects for visit appointments or at a later date to inform them of newly received information. Information collected will be labeled with a study number and will be entered in to a secure MRN server, and/or the COINS database on a secure HIPAA compliant cloud-based server. Data linking scan to identity will be maintained at the Mind Research Network indefinitely allowing the neuroradiologist to compare future scans with previous ones. Research data (not including scan data) will be de-identified after the study is complete and closure documents are submitted to the UNM IRB.

Electronic Data: Collaborative Neuroinformatics Suite (COINS). This cloud-based neuroimaging and neuropsychology software suite offers versatile, automatable data upload/import/entry options, rapid and secure sharing of data among PIs, querying and export all data, real-time reporting, and HIPAA and IRB compliant study-management tools suitable to large institutions as well as smaller scale neuroscience and neuropsychology researchers. Network is accessed on a secure MRN server, and/or a HIPAA compliant cloud-based server which has firewalls in place. Controlled access is granted to only study team members.

As per NIMH mandate, the de-identified data will be submitted to the National Institute of Mental Health Data Archive (NDA). NDA is a data repository run by the National Institute of Mental Health (NIMH) that allows researchers studying mental illness to collect and share de-identified information with each other. During and after the study, the UNM research team will send de-identified information to NDA. Other researchers nationwide can then file an application with the NIMH to obtain access to de-identified study data for research purposes. Experts at the NIMH who know how to protect health and science information will look at every request carefully to minimize risks to your privacy. In addition, de-identified information will be available at the Mind Research Network Data Sharing Repository for future research. Both the NDA and Mind Research Network Data Repositories are clearly described in the "Data Sharing" section of the consent form.

18. Risks to Subjects

Participation in this study may involve minor risks and/or discomforts associated with possible breach of confidentiality risk, neuropsychological testing, MRI, and lower amplitude ECT.

Due to the coronavirus public health crisis, participants will receive regular COVID-19 testing as part of their standard ECT treatment procedure. Participation in this study may entail increase risk of exposure to COVID-19 during interactions with research staff. However, research staff adhere to all safety operating procedures required by UNM HSC, NMDOH and the CDC.

MRI: Radio and magnetic waves associated with MRI scans are not associated with any known adverse effects. MRI is non-invasive, non-contrast, and considered minimal risk by the FDA and OHRP. However, the scanner is a large magnet, so it could move objects containing ferrous metal in the room during the scan. All participants are screened using the MRI safety screening form prior to be being scanned. Participants with any MRI scanning contraindications will be excluded from study participation. Participants may be bothered by feelings of claustrophobia (uncommon). The MRI also makes loud 'drum' beating noises during the study. Headphones are provided for protection. Rarely, large or recent tattoos can heat up during an MRI scan and cause skin irritation like a sunburn (uncommon). No long-term harmful effects from MRI are known. However, since the effect of MRI on early development of the fetus is unknown, participants who are pregnant will not be allowed to go in the MRI. Females 18 years of age or older who suspect they may be pregnant will be asked to take a urine pregnancy test before being allowed to participate in the study. The test results will only be shared with participant. The MRI risks include identification of incidental findings and potential cost for follow-up or clinical scans.

Neuropsychological tests and clinical assessments: The neuropsychological tasks involved in the protocol entail no foreseeable risk, besides perhaps fatigue or mild to moderate demands on attention and cognition.

19. Potential Benefits to Subjects

The potential benefits of the proposed research for the research participants are minimal. Any abnormal findings on structural MRI scans will be reported to the participant and/or their doctor per the participant's request. This may lead to early detection of previously unknown abnormalities. However, for the large majority of participants, the proposed research will not have any benefit.

20. Recruitment Methods

The UNM ECT Treatment Program receives referrals from inpatient and outpatient providers at the UNM Mental Health Center. The treatment team will clinically determine who will be eligible for the study and document this in the subject's study records. The research team will only approach patients for the study protocol who speak English and have been identified by the primary treatment team. Patients diagnosed with Major Depression are eligible for ECT treatment will be recruited from the UNM ECT Treatment Program.

21. Provisions to Protect the Privacy Interests of Subjects

The Center for Psychiatry Research handles all confidential data carefully and works to maintain subject privacy and confidentiality. From the standpoint of privacy and confidentiality, the subject's welfare will be safeguarded by responsible, systematically controlled procedures in the collection of information for both clinical and research purposes. In terms of privacy, subjects will first arrive at the research clinic, housed in UNM HSC Center for Psychiatric Research in the Neurobiology Building, 1101 Yale Blvd NE, 2nd floor. Interaction with subjects will be in the Psychiatry Research Clinic and will only be with relevant staff and/or with family members that they choose to be present. Interviews are held in closed door offices and will be conducted in a manner most comfortable to subjects. Subjects may refuse to answer any question at any time. Recorded information for research purposes will be identified only by subject initials and a study code number. Subject data will be kept in locked cabinets in the research clinic with limited access granted only to designated research personnel. These processes will be in place throughout the entire research process, from initial consenting to research, through research procedures, and follow-up. The study PI will maintain confidentiality of all records to the extent permitted by applicable laws. Records may be inspected by representatives of the study sponsor, the HRRC and other regulatory agencies. If results are presented or published, subjects' identities will remain confidential.

22. Economic Burden to Subjects

The costs of the MRIs and office visits required by the research will be covered by the study. Subjects will be not placed under economic burden due to this trial.

23. Compensation

This study will require attending three visits that will last approximately 2.5 hours for each. Subjects will be compensated $50.00 for completion of each visit (total subject compensation will be $150 for the three assessment time-points). Subjects will receive compensation ($50 merchandise card) at each visit. Social security numbers will not be required for subject payment. The cost of gas/transportation and the inconvenience of participating in this study, make these compensation rates fair and reasonable. Subjects will be reimbursed an additional $50 merchandise card for participating in the optional EEG to offset additional set-up time.

24.Compensation for Research-Related Injury

UNMHSC will provide subjects with emergency treatment, at their own cost. No commitment is made by the University of New Mexico Health Sciences Center (UNMHSC) to provide free medical care or money for injuries to participants in this study. In the event that you have an injury or illness that is caused by a subject's participation in this study, reimbursement for all related costs of care will be sought from their insurer, managed care plan, or other benefits program. If the subject does not have insurance, they may be responsible for the costs. Subjects will also be responsible for any associated copayments or deductibles required by their insurance.

25.Consent Process

Discussion of the proposed study will occur separate from the evaluation for the ECT procedure. Potential subjects will have ample time to ask questions regarding the nature of this study and will be clearly informed that this imaging investigation is optional. Informed consent will be discussed with each participant with plenty of opportunities to ask questions. The study PI (Abbott) or Co-PI (Quinn), board-certified psychiatrists with additional fellowship training and certification, will assess decisional capacity for each subject during the consent process. The PI's have extensive experience with the assessment of decisional capacity in both research and clinical domains. All subjects must have decisional capacity to consent to this protocol. Prior to discussion of research participation, the UNM ECT service (Board certified psychiatrists) will assess decisional capacity for the procedure. This assessment will include decisional capacity (ability to communicate choice, appreciate risks/benefits, reason, and manipulate information) and voluntarism capacity.

26.Documentation of Consent

Notes will be kept documenting the informed consent process. Narrative forms will be securely filed with other subject information to document each visit and contact, in addition to required study measures and procedures. Subjects will be given a copy of their signed consent form and HIPAA. A member of the research team will review the HIPAA authorization during the consent.

27.Study Test Results/Incidental Findings

Subjects who receive abnormal MRI scan findings by the neuroradiologist will be notified of an official report by e-mail letting the participant know new results are available and the study PI will communicate the results to the patient. The participant can securely log in to the Mind Research Network COINS homepage to access their MRI radiology report. No sensitive or identifying information is sent via e-mail. If an abnormality that requires follow-up is identified, such as a Doctor Referral recommendation, a hard copy of the report will be mailed to the participant in addition to the e-mail notification. With the patient's permission, the study PI will communicate the results to the patient's primary care providers.

28. Progress or Results with Subjects

The MRI scan is being done to answer research questions, not to examine the subject's brain for medical reasons. This MRI scan is not a substitute for a clinical scan (the type a doctor would order). The research scan may not show problems that may be picked up by a clinical MRI scan. However, all research MRI scans will be read by a neuroradiologist (a doctor with experience reading MRI scans) unless they have been scanned at MRN in the previous six months. If the scan is read, the subject will receive the official report by email. If we find an abnormality that requires urgent follow-up, we will contact the subject by phone to help answer questions and get the right follow-up care. The MRN Medical Director or the research team is always available to answer any questions you may have about the subject's scan.

29.Inclusion of Vulnerable Populations

Sample inclusion will not include gender restrictions. It is expected that our sample will reflect the gender distribution of our ECT service over the last 5 years. Recruitment will reflect the demographics of the state of New Mexico. Prisoners will be excluded from the study. The age range of 50 to 80 years was selected because to limit the variability of age-related volume changes. Subjects with pre-existing diagnoses of neurodegenerative diseases or cerebrovascular pathology will be excluded. However, some older subjects may have significant cognitive deficits prior to treatment related to their depressive episode ("pseudo-dementia"). These subjects may not have decisional capacity for this investigation but are representative of a community sample receiving ECT in this age range. Dr. Abbott (PI) and Quinn (Co-PI) will assess decisional capacity of all subjects participating in this investigation. Subjects that do not have decisional capacity for this investigation will be able to participate in this research if they can assent to the procedure and a legally authorized representative (court appointed mental health treatment guardian) consents to the research protocol.

30.Community-Based Participatory Research

N/A

31.Research Involving American Indian/Native Populations

The proposed research inclusion criteria will be open to all patients with major depressive disorder meeting the inclusion criteria including the clinical indication for ECT. The UNM ECT service is part of a tertiary referral service and the demographics of this service reflect the state of New Mexico. This investigation will not have targeted recruitment outside of routine clinical referrals to the UNM ECT service.

32. Transnational Research

N/A

33. Drugs or Devices (see section 9. Resources Available)

The research involves an investigational device. The Mecta Spectrum 5000Q paired with Soterix Medical 4X1 HD-ECT Multi-Channel Stimulation Interface is intended to reduce ECT current amplitude for amplitude-seizure titration and has received approval from the Food and Drug Administration (refer to "supporting documents"). Digitimer DS8R Biphasic Constant Current Stimulator will be used for motor titration during the second treatment.

These devices will be solely handled and operated by credentialed UNM ECT providers at the UNMH Post Anesthesia Care Unit (inpatient) or UNM Outpatient Surgical Imaging Services (outpatient).

Additionally, the research proposal will use DC-EEG device. The SMARTING (https://mbraintrain.com/smarting/) is a small, mobile EEG device that incorporates motion sensors that detect head and body movements. This EEG system will include a 24-channel recording cap. EEG data will be wirelessly recorded to mobile app and is capable of measuring low frequency EEG (< 0.01) pertinent for this proposal.

34. Principal Investigator's Assurance

By submitting this study in the Click IRB system, the principal investigator of this study confirms that:

☒ The information supplied in this form and attachments are complete and correct.

☒ The PI has read the Investigator's Manual and will conduct this research in accordance with these requirements.

☒ Data will be collected, maintained and archived or destroyed per HSC Data Security Best Practices, including:

1. **Best Practice for data collection** is for it to be directly entered onto a data collection form that is in a secured access folder on an HS drive behind a firewall, or in a secure UNM Data Security approved system such as RedCap.
2. **Data collection of <u>de-identified data</u>**, if done in a clinical setting or other setting that does not allow direct entry into a secured system, may be done temporarily using a personal or university owned electronic storage device or hard copy document. **The**

important security safeguard is that no identifiers be include if the data is entered or stored using an untrusted device or storage.

3. **Permanent (during data analysis, after study closure**) storage must reside on HSC central IT managed storage. Processing of data (aggregation, etc.) are to be carried out in such a way as to avoid creating/retaining files on untrusted storage devices/computers. Trusted devices are HSC managed and provide one or more of following safeguards: access logs, encryption keys, backups, business continuity and disaster recovery capabilities.
4. **Alternate storage media** must be approved by HSC IT Security as meeting or exceeding HSC central IT provided security safeguards.

35. CHECKLIST SECTION

This section contains checklists to provide information on a variety of topics that require special determinations by the IRB. Please complete all checklists relevant to your research.

36. Partial Waiver of Consent for Screening/Recruitment

N/A

37. Partial Waiver of HIPAA Authorization for Screening/Recruitment

N/A

38. Waiver of Documentation of Consent

N/A

39. Alteration of Consent

N/A

40. Full Waiver of Consent/Parental Permission

N/A

41. Full Waiver of Consent/Parental Permission (Public Benefit or Service Programs)

N/A

42. Full Waiver of HIPAA Authorization (Checklist)

N/A

43. Other Waiver Types (Checklist)

N/A

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44. Vulnerable Populations (Checklist)

A. Adults with Cognitive Impairments

1. Describe why the objectives of the study cannot be met without inclusion of adults with cognitive impairments.

Older subjects with major depressive disorder often present with significant cognitive impairment. In the context of ECT response, these patients often have resolution of depression-related cognitive impairment.

2. Describe how capacity to consent will be evaluated.

   Prior to discussion of research participation, the UNM ECT service (Board-certified psychiatrists) will assess decisional capacity for the procedure. This assessment will include decisional capacity (ability to communicate choice, appreciate risks/benefits, reason, and manipulate information) and voluntarism capacity. If the patient does not have decisional capacity, the subject will not be able to participate in this research.

3. If subjects may regain capacity to consent, or if subjects may have fluctuating capacity to consent, describe your plans to evaluate capacity to consent throughout the research and to obtain consent to continue participation if capacity is regained.

   In the context of fluctuating consent capacity, the PI and Co-PI will reassess decisional capacity at each study visit. If the subject maintains the minimal threshold to continue with the proposed study, the study team will also include input from surrogate decision maker (power of attorney and/or treatment guardian) to provide additional safeguards. If the subject no longer maintains decisional capacity at a study visit, the subject will be withdrawn from the protocol.

4. Describe your plans, if any, to provide information about the research to subjects and the steps you will take to assess understanding.

   The study PI (Abbott) and Co-PI (Quinn) are board-certified psychiatrists with fellowship training in geriatric psychiatric and psychosomatic medicine and will be involved with the consent process for all study participants. They will assess decisional capacity at all three study time points.

5. Describe your plans to obtain assent, including whether assent will be obtained from none, some, or all subjects.

   All subjects must have decisional capacity to consent to this protocol.

6. Describe why risks to subjects are reasonable in relation to anticipated benefits to the subjects.

   The risks of low-amplitude seizure and motor titration will be minimal relative to the traditional (higher) ECT amplitudes. The experimental portion of this protocol is relevant only to the first treatment with the remaining treatments completed at the traditional 800 mA amplitudes. Subjects will also receive more comprehensive clinical and neuropsychological assessments by participating in this research protocol relative to routine clinical care.

7. If this study involves a health or behavioral intervention, describe why the relation of the anticipated benefit to the risk of the research is at least as favorable to the subjects as that presented by alternative procedures.

   This investigation proposes use amplitude titration relative to the traditional pulse-number based titration and fixed amplitude ECT. This difference is only relevant to the first treatment. The remaining treatments will be completed with traditional 800 mA ECT.

8. Describe your plans for monitoring the well-being of subjects including any plans to withdraw subjects from the research if they appear to be unduly distressed.

   Subjects that appear to be distressed will be encouraged to withdraw from the study protocol. If subjects appear to be unduly distressed, the study PI will withdraw these subjects from the protocol. Data regarding subject drop-out will be documented and presented to the DSMB.

B. Children
N/A

C. Pregnant Women and Fetuses
N/A

D. Neonates of Uncertain Viability or Nonviable Neonates
N/A

E. Nonviable Neonates
N/A

F. Biomedical and Behavioral Research Involving Prisoners
N/A

45.Medical Devices (Checklist)

Complete this checklist if the research evaluates the safety or effectiveness of a medical device. If more than one medical device is being evaluated, provide the requested information for each.

A. Device Name: Mecta Spectrum 5000Q paired with Soterix Medical 4X1 HD-ECT Multi-Channel Stimulation Interface

B. Manufacturer: Soterix Medical
237 West 35th Street
Suite 1401
New York, NY 10001
Contact: Dr. Abhishek Datta
Email: adatta@soterixmedical.com

C. Does the research involve a Significant Risk Device under an IDE?

☒ Yes. Include documentation of the FDA approval of the IDE with your submission. *Acceptable methods of documentation include: (1) FDA letter noting IDE number and approval status; (2) Industry sponsor letter noting IDE number and FDA approval status; or (3) FDA-approved industry sponsor protocol with IDE number noted*

☐ No

D. Is the research IDE-exempt?

☐ Yes. Include a FDA letter with your submission noting the determination that the research is IDE-exempt or a letter from the sponsor (or sponsor-investigator) justifying why they believe the research is IDE-exempt*.

☒ No

E. Does the research involve a Non-Significant Risk (NSR) Device?

☐ Yes. Include a FDA letter with your submission noting the determination that the research is NSR or a letter from the sponsor (or sponsor-investigator) justifying why they believe the research is NSR**.

☒ No

* This FDA guidance includes a description for when a device study is exempt from the IDE requirements:
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM127067.pdf

**This FDA guidance includes information on how to differentiate between Significant Risk and Non-Significant Risk device studies:
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf

46.Export Control (Checklist)

N/A

47.Data Transfer/Sharing (Checklist)

Complete this checklist if the research involves transferring/sharing of data with an external entity (institution, company, etc.).

A. Will data be transferred/shared with an external entity (institution, company, etc.)?

☒ Yes

☐ No. **The remainder of this section does not apply.**

B. Indicate if the data is incoming and/or outgoing: Outgoing

C. Provide the name of the entity that data will be transferred/shared with: De-identified clinical and imaging data will be uploaded to the National Institute of Health National Data Archive at 6-month intervals. This is an NIH requirement.

D. Provide the contact name, email and phone number with whom data is being transferred or shared with: https://nda.nih.gov

E. Who is responsible for transmission of the data? Study PI (Abbott) and team

F. Who is responsible for receiving the data? NIMH Data Archive

G. Describe how the data will be transferred/shared. Please note data cannot be transferred/shared without assistance from UNM HSC IT. **Requesting HSC Central IT Transfer is detailed on the Sponsored Projects website:** De-identified data will be uploaded to NIMH Data Archive through the COINS (https://coins.trendscenter.org) system.

H. For data being transferred/shared with outside locations or entities, describe the following:
- Where is data storage and how will it be maintained in a secure manner (i.e. encryption, password protection, use of Qualtrics or REDCap, etc)? https://coins.trendscenter.org. Data is encrypted and password protected.
- What is method in which data will be collected and stored (i.e. electronic, hard copy, etc)? Data will be initially recorded in paper charts and then electronically uploaded to COINS site. The data will be then be uploaded at 6-month intervals from COINS to the NIMH Data Archive.
- How long will the data be stored? *Paper charts will be kept for the duration of the study. COINS and NIMH Data Archive (de-identified data) will be kept indefinitely.*
- Who will have access to data? *Study team will have access to the COINS data; Other investigators must access NIMH Data Archive through established protocols (https://nda.nih.gov/get/access-data.html).*

I. Please list all specific data elements, variables, etc. to be sent out and/or received. Indicate if the data contain identifiers and health information. Please note that identifiers that MUST be removed to make health information de-identified are as follows: Names, All geographic subdivision smaller than a State, All elements of year (except year), Telephone, Fax numbers, E-mail addresses, Social Security, Medical record number, Health plan beneficiary, Account numbers, Certificate/license numbers, Vehicle identifiers and serial numbers, Device identifiers and serial numbers, Web URLs, IP address numbers, Biometric identifiers, full face photographic images, and Any other unique identifying number, characteristic or code.) All identifying elements outlined above will not be included in COINS or uploaded to the NIMH Data Archive. All subjects participating in this protocol have provided permission for the transfer of their de-identified data to the NIMH Data Archive.

J. If the research requires the access, use, or disclosure of any of the 18 individually identifiable protected health information (PHI) identifiers that can be used to identify,

contact, or locate a person (e.g., name, medical record number, etc.), are the subjects going to consent to or authorize the disclosure of their individually identifiable health information? Not applicable.

a. ***Or*** is HIPAA authorization altered or waived? Not applicable

K. What is the classification of the data: de-identified, limited data set, protected health information, or other type? De-identified.

L. Does the request to transfer/share data include clinical data that belongs to the UNM Health Systems? The included information will be generated for research purposes only (including imaging data acquired at Mind Research) and does not belong to UNM.

M. Does the data to be transferred/shared include information about patients seen at external health system or at a third party medical provider? Not applicable.

N. Is the external entity a "covered entity"? Not applicable.

O. Is the data that is going to be transferred/shared owned or partially owned by another party or have any type of restrictions including regulatory restrictions (i.e. HIPAA, FERPA, etc.)? De-identified data transferred to the NIMH Data Archive (NDA) will be coded using a unique code known as a Global Unique Identifier (GUID). Use of the GUID minimizes risks to study participants because it keeps one individual's information separate from that of another person without using names, addresses, or other identifying information. The unique code also allows the NDA to link together all submitted information on a single participant, giving researchers access to information that may have been collected elsewhere. The GUID is a computer-generated alphanumeric code [example: NDA-1A462BS] that is unique to each research participant (i.e., each person's information in the NDA—or each subject's record—has a different GUID). The process of assigning a GUID prevents direct identifiers from ever being transmitted or stored in the NDA. We will ensure that no direct identifiers are transmitted in this process.

P. Is the data publicly available? If yes, please provide details: As per the NIMH Data Archive site, "Summary information on the data shared in NDA is available in the NDA Query Tool without the need for an NDA user account. To request access to record-level human subject data, you must submit a Data Access Request.

Q. Does the data include information about substance abuse treatment, sexually transmitted diseases, genetic testing results, HIV/AIDS testing results, and/or mental health? Mental health data will be included with this data.

48. Specimen Transfer/Sharing (Checklist)

N/A