MEDICAL FACULTY ASSOCIATES

THE GEORGE WASHINGTON UNIVERSITY

RESEARCH PROTOCOL

Low Frequency Electrical Stimulation of the Fornix in Intractable Mesial Temporal Lobe Epilepsy (MTLE)

GWU IRB Reference number: {111239}

Principal Investigator: Mohamad Koubeissi, MD Phone: (202) 741- 2719

Study Coordinator: Radwa Aly Phone: (202) 677-6210

Sponsor: George Washington University Medical Center

TITLE: Low Frequency Electrical Stimulation of the Fornix in Intractable Mesial Temporal Lobe Epilepsy (MTLE)

SYNOPSIS:

Title	Low Frequency Electrical Stimulation of the Fornix in Intractable Mesial Temporal Lobe Epilepsy (MTLE)
Purpose	• Develop a dual-site, multidisciplinary clinical research protocol to evaluate the safety and tolerability of low frequency electrical stimulation of the fornix in patients with intractable Mesial Temporal Lobe Epilepsy (MTLE) • Enroll up to 16 participants at one center into a single blinded study to evaluate the safety and tolerability of low frequency stimulation of the fornix (LFSF) in intractable MTLE. • Secondary aims will assess psychiatric changes, seizure frequency changes, and quality of life.
Study Design	Single-site, Single-blinded, multi-dose protocol
Sample Size	The study will recruit up to 16 participants
Study Sites	2
Participant Selection Criteria	**Inclusion Criteria:** • Participants are between the ages of 18 -65 years of age

	• Participants must have had a non-invasive video-EEG monitoring revealing seizure semiology and ictal EEG consistent with unilateral or bilateral MTLE • Participants must have tried and failed two trials of antiepileptic drugs (AEDs) • Participants may have lesional or non lesional hippocampi, as evidenced by brain MRI acquired within the previous two years. • Participants are prescribed and taking at least one AED at the time of study entry • Study participants will have intractable (MTLE) with a seizure frequency of at least 1/month averaged over the preceding 6 months prior to enrollment, including maximum seizure-freedom periods of no more than 60 days. • Participants must have a platelet count greater than 125,000 per cubic millimeter and prothrombin time (PT) and activated partial thromboplastin time (aPTT) within normal limits at the visit prior to surgery **Exclusion Criteria:** • Progressive neurological or medical diseases, such as brain tumors or neurodegenerative disease or cancer • Non-compliance with antiepileptic medications as demonstrated by the medical record • Any conditions interfering with electrode implantation • Any non-epileptic seizures • Inability or unwillingness to complete neuropsychological tests or complete seizure diaries • Current drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements • Pregnant, or planning to become pregnant*

	• Participation in another research trial where the participant was treated with another investigational drug or device within 30 days prior to enrollment of study • IQ showing a General Ability Quotient of less than 70. The score excludes the contribution of working memory and processing speed (which are areas of cognitive functioning that are vulnerable to numerous influences including seizures, fatigue and effects of AEDs). • Inability or unwillingness of individual or legal guardian/representative to give written informed consent • Participants who have changes to their antiepileptic medications during the baseline phase (as they will need to repeat the baseline phase) • Subjects with history of status epilepticus within the preceding year • History of psychiatric illness necessitating hospitalizations • Subjects who have any of the following implanted devices: aneurysm clips, cardiac pacemaker or defibrillator, cochlear implant, spinal cord, DBS, or vagal nerve stimulator. • Co-morbid conditions that would interfere with study stimulation activities or response to treatment, which may include: o Neoplasm with life expectancy < 5 years o Severe chronic pulmonary disease o Local, systemic acute or chronic infectious illness o Life threatening cardiac arrhythmias o Severe collagen vascular disorder o Kidney failure or other major organ system failures

Specific Aims

Statistical Analysis

The statistical methods to be used to analyze the primary and secondary aims of the trial:

Primary outcome:

Because we are assessing AVLT score at multiple instances within subjects (i.e. repeated measures), we will use generalized estimating equations (GEE) to test for statistically significant changes in AVLT score, controlling for within-subject correlation. Post-stimulation AVLT scores will be entered into the GEE model as the dependent variable values, and stimulation intensity levels and stimulation frequency levels will be viewed as fixed factor levels. Pre-stimulation AVLT score will also be entered as an independent variable.

Primary statistical aim: Assess whether or not stimulation at each combination of frequency levels 1hz or 5hz and crossed with intensity levels 2mA, 4mA, or 8mA leads to reduce AVLT score by at least the a priori-defined minimum clinically-significant change of 10 points from control period, defined as the presurgical neuropsychological scores. Data will be comprised of measurements taken immediately after the 2-month stimulation periods.

The GEE model will be built to test these hypotheses using the identity link function and assuming Gaussian error distributions. If AVLT scores do not appear to be approximately normally distributed, we will attempt to transform the scores. Exchangeable correlation matrix structure in the GEE model will be used to indicate the degree of within-subject correlation between AVLT scores. This correlation structure appears to fit other longitudinal models involving AVLT scores. Post-hoc, we will reassess statistical significance of stimulation-induced changes in AVLT score using alternative GEE correlation matrix structures (stationary and autoregressive). The missing completely at random (MCAR) assumption will be explored such as through logistic regression models, to assess if missing-ness of a data value may be related to previously observed AVLT scores from a same subject, or the experimental factors. Mixed models, such as random intercept, will be fit as well, which will be important if the missing at random (MAR) assumption appears more plausible, and inferential results compared with GEE-based findings, and with models that relax the MAR assumption, such as shared parameter models.

Secondary analyses: The experimental design allows for estimation of carryover effects through implementation of rest periods following each period of stimulation. Using similar analytic approaches as above, we will test in an exploratory manner if there are differences in AVLT scores between rest periods following stimulation and the control period. This will give insight into whether carryover effects after two months of rest differ by treatment level.

The statistical basis for the sample size calculation:

Based on published findings 15, 17, we define clinically significant change in AVLT score to be a reduced score of at least one standard deviation. Based on our own available longitudinal test data, we estimate the expected standard deviation (SD) of AVLT score to be at most ten points, and within-subject correlation of AVLT to be 0.65. Using these values (SD and within-subject correlation), for the six contrasts of interest, we estimate a minimum sample size to be able to detect with 80% power under two-sided Type I error alpha = 0.0083 (Bonferroni correction for 6 tests). Simultaneous Type I error will be 0.05, and a 20% dropout will be supposed. Preliminarily, we project a need for approximately 16 subjects. Please note that these projections will be more carefully derived for the full application, such as via simulation.

Background and Significance

PART 1: REPORT OF PRIOR INVESTIGATIONS

General Introduction

Temporal Lobe Epilepsy

Overview

Epilepsy affects 3 million people in the United States, with associated health care costs of $12.5 billion/year. Focal seizures originate from one spot in the brain, called the seizure focus. If focal seizures are medically intractable, patients should undergo an evaluation for epilepsy surgery. The evaluation aims at identifying the seizure focus, but surgical removal is done only if the seizure focus is in an area that is not essential for speech, movement, memory, or other important functions. Mesial temporal lobe epilepsy (MTLE) is the most common form of focal epilepsy in

adults. One third of temporal lobe epilepsy (TLE) is intractable, posing high risks of cognitive decline and increased mortality, in addition to social, psychological, and economic burdens.

The hippocampus, an elongated structure within the temporal lobe, is crucial for memory processing, but is also the source of most temporal lobe seizures. In patients with intractable TLE, resection of the temporal lobe, including the hippocampus, has higher chances of stopping seizures than medical therapy, but with the obvious risk of memory decline, especially in patients with normal brain MRI, including intact-looking hippocampi (non-lesional MTLE). Deep brain stimulation (DBS) offers a new therapeutic avenue for patients who are not good surgical candidates, as it aims to decrease or stop seizures, but preserve or improve memory.

Importance of the problem

Epilepsy is defined as recurrent, unprovoked seizures caused by abnormal electrical disturbances in the brain. Seizures may manifest as a variety of symptoms ranging from transient fear and sensory phenomena to loss of consciousness and convulsions. Epilepsy is one of the most prevalent neurological disorders affecting 3 million people in the U.S., with associated health care costs of $12.5 billion/year (Begley, Famulari et al. 2000). While 60-70% of all patients with epilepsy respond to antiepileptic medications (Schmidt 2009), drug treatment is often ineffective in mesial temporal lobe epilepsy (MTLE) (Bartolomei, Wendling et al. 2001; Pallud, Devaux et al. 2008), and medically-intractable epilepsy causes disability with a burden that is equivalent to that of breast and lung cancer, according to the World Health organization (Engel, Wiebe et al. 2003).

MTLE, the most common cause for intractable focal epilepsy (Engel 1996) and the most frequent indication for epilepsy surgery (Benifla, Otsubo et al. 2006), results in psychiatric co morbidities (Schmidt 2009), cognitive decline, and increased mortality (Langfitt and Wiebe 2008) with associated momentous social and economic burdens (Campos and Wiebe 2008). MTLE originates from the hippocampus, a structure that is critical to memory function. A prospective, randomized clinical trial showed that when participants with MTLE fail initial medication trials, continued medical therapy can achieve seizure freedom in only 8%, whereas surgical resection of the temporal lobe, including the hippocampus, renders 58% of participants seizure free (Wiebe, Blume et al. 2001).

The significant benefit of surgery (Wiebe, Blume et al. 2001; Clusmann, Schramm et al. 2002), however, must be weighed against the risk of postoperative memory dysfunction. The risk of memory decline after hippocampal resection depends on the structural integrity of the hippocampus and its degree of contribution to memory function prior to surgery, typically assessed using thorough neuropsychological evaluations. Thus, a non-lesional hippocampus on MRI and good preoperative memory function exclude MTLE participants from temporal lobectomy because of the high-risk of postoperative memory decline (Trenerry, Jack et al. 1993; Bell, Rao et al. 2009). This underlies the need to pursue an intervention that will control disabling hippocampal seizures without adversely disrupting memory functioning.

Deep Brain Stimulation

In recent years, deep brain stimulation (DBS) has been established as an effective treatment for movement disorders, and has proven to be a safe and effective treatment over the long term (Witt, Daniels et al. 2008). In addition to the treatment of movement disorders, pain syndromes, and psychiatric disorders, deep brain stimulation also has the possibility of becoming an innovative treatment for epilepsy (Krauss and Koubeissi 2007). With about one-third of patients with epilepsy who continue to be subject to seizures even after attempted treatment with a wide variety of anticonvulsive drugs, there continues to be great interest in using deep brain stimulation for treatment of intractable epilepsy (Al-Otaibi, Hamani et al. 2011). While the success of DBS in epilepsy has been limited, it must be noted that most DBS trials in epilepsy have used high frequency stimulation (HFS), often in the range of 100 Hz or more (Fisher, Uematsu et al. 1992; Velasco, Carrillo-Ruiz et al. 2005; Velasco, Velasco et al. 2007; Velasco, Velasco et al. 2007; Fisher, Salanova et al. 2010). Thus, stimulation at frequencies of <10 Hz continues to be a potentially efficacious, uninvestigated method for treating epilepsy.

Mechanisms

While HFS has multiple possible mechanisms of action including activation of efferent projections, reducing deleterious signals in neural circuits by reducing “information content”, and activation of presynaptic inhibitory inputs (Dorval, Russo et al. 2008), Low frequency stimulation

(LFS) has been shown to inhibit abnormal excitatory activity by such mechanisms as increasing the threshold of action potential firing by long term depression (Fujii, Saito et al. 1991; Albensi, Ata et al. 2004; Schrader, Stern et al. 2006; Yang, Jin et al. 2006), or increasing GABA–mediated inhibition (Kinoshita, Ikeda et al. 2005). Moreover, LFS of either the kindling focus(Velisek, Veliskova et al. 2002) or areas that participate in seizure spread (Yang, Jin et al. 2006) delays seizure development in the amygdaloid kindling model, which is a model of recurrent hippocampal seizures in rats that result from electrical kindling of the amygdala. Even in fully kindled animals, preemptive LFS at the kindling focus dramatically decreases stage 5 seizures (Goodman, Berger et al. 2005). Finally, LFS of the ventral hippocampal commissure (a white matter tract that connects the hippocampi) reduces seizures in a genetic model of epilepsy in mice (Kile, Tian et al. 2010), as well as in the amygdaloid kindling model in rats(Rashid, Pho et al. 2011).

In addition to animal data (Albensi, Ata et al. 2004; Goodman, Berger et al. 2005; Kile, Tian et al. 2010), the efficacy of LFS has been suggested in humans (Yamamoto, Ikeda et al. 2002; Schrader, Stern et al. 2006) and illustrated in our preliminary data. LFS is attractive for clinical implementation since the duty cycle of the stimulation is very low implying less electric current injection - with less charge density on target tissue and electrodes - and longer battery life. This has led to a trial of short term low-frequency stimulation of the fornix (LFSF) in patients with intractable MTLE (see proof-of-principle data), and we are currently ready to further advance the development of this new therapy for epilepsy.

Thus, the current proposal is a classic translational research project, demonstrating a clear path from the laboratory to bedside. If successful, this new therapy will be of great value to patients with medically intractable MTLE. The proposed phase I study will lay the groundwork for a larger randomized, controlled clinical trial that will assess efficacy as a primary measure. Our preliminary results suggest that LFSF is safe and tolerable, and could have a remarkable therapeutic effect. This procedure is indicated for use in patients who have intractable mesial temporal lobe epilepsy (defined as failure of 2 antiepileptic medications to control seizures) and who have normal brain MRI or evidence of hippocampal sclerosis.

The investigation will be conducted at George Washington University. This Epilepsy Center is internationally renowned for its experience in intracranial monitoring and epilepsy surgery. It is a multidisciplinary program consisting of adult epileptologists, neurophysiologists, advanced care nurses, and neurosurgeons, including experts in Deep Brain Stimulation (DBS).

The primary site at George Washington University, in Washington DC has a large referral base from on-site internal medicine, family medicine, and general neurology clinics, and multiple off site clinics.

Proof of Principle Data

The preliminary data included in the original submission has been updated, analyzed and published in the Annals of Neurology. We have included a PDF copy of that paper as part of the current amendment. Additionally, below are the information and figures that summarize the preliminary data of two subjects that have completed the current protocol under this IDE.

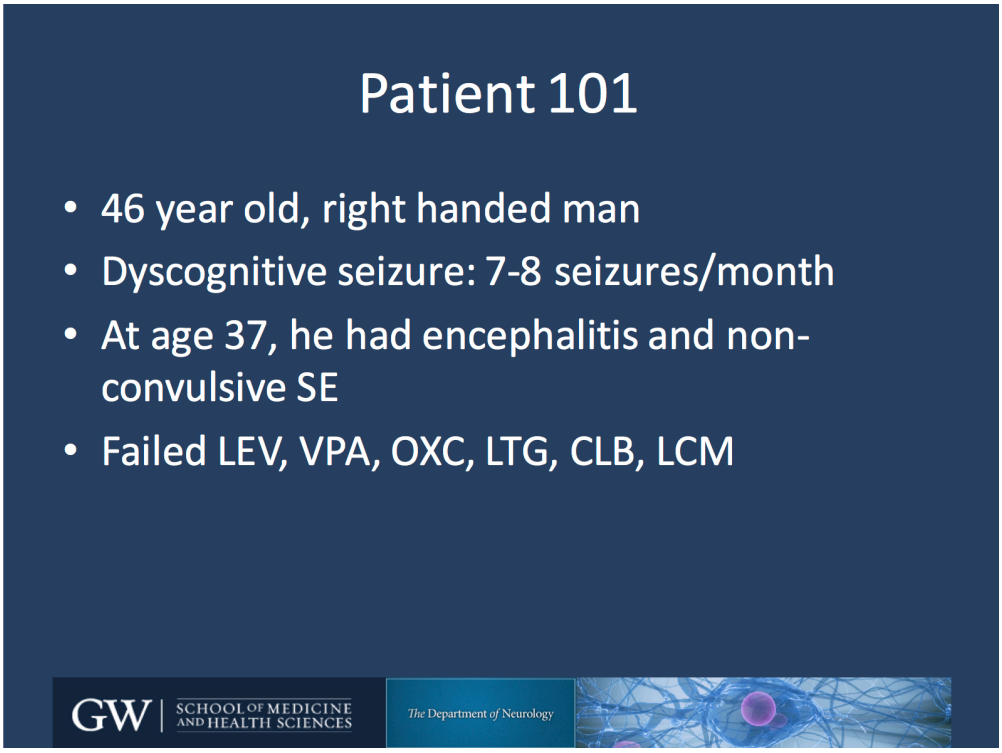

Figure 1: Subject 101 baseline history

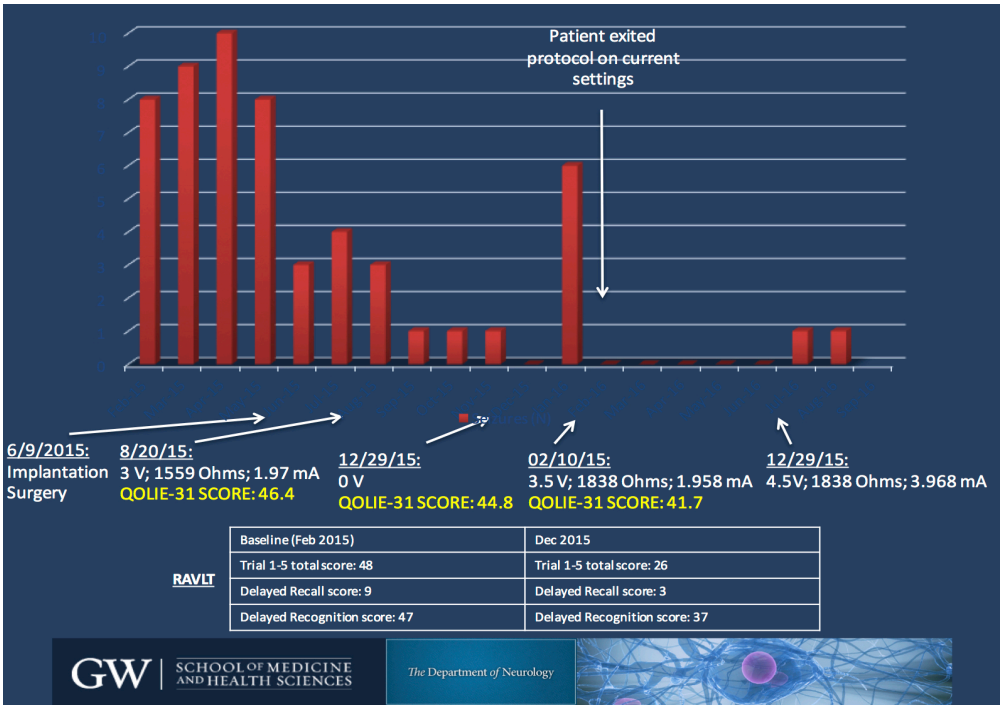

Figure 2: Subject 101 baseline and follow-up seizure frequency, QOLIE-31 and RAVLT scores

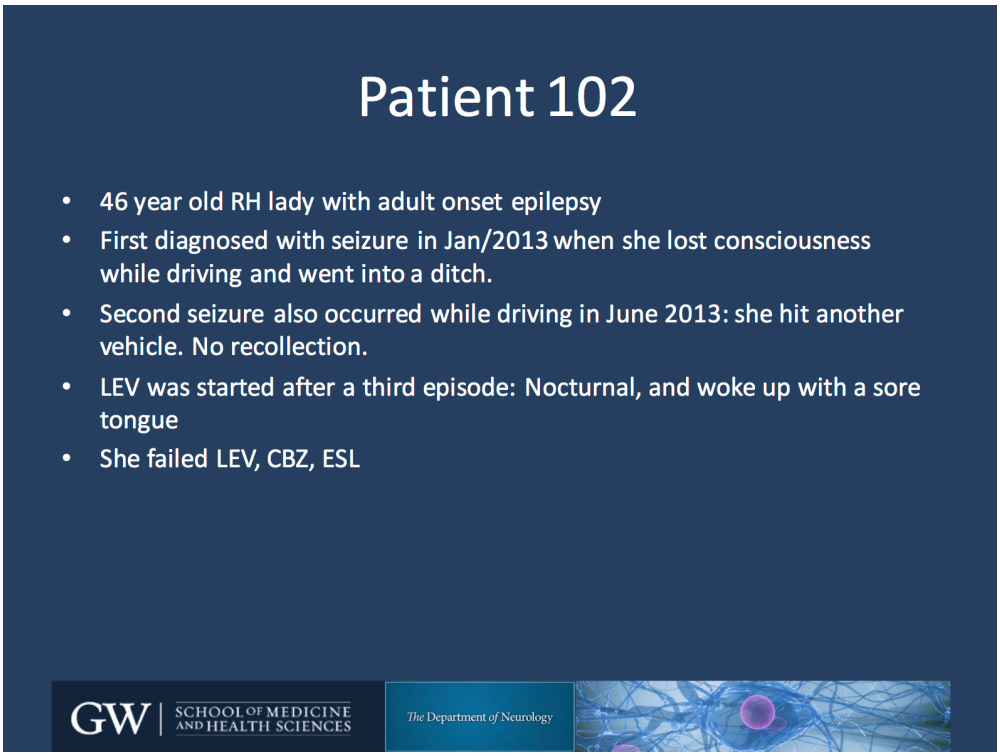

Figure 3: Subject 102 baseline history

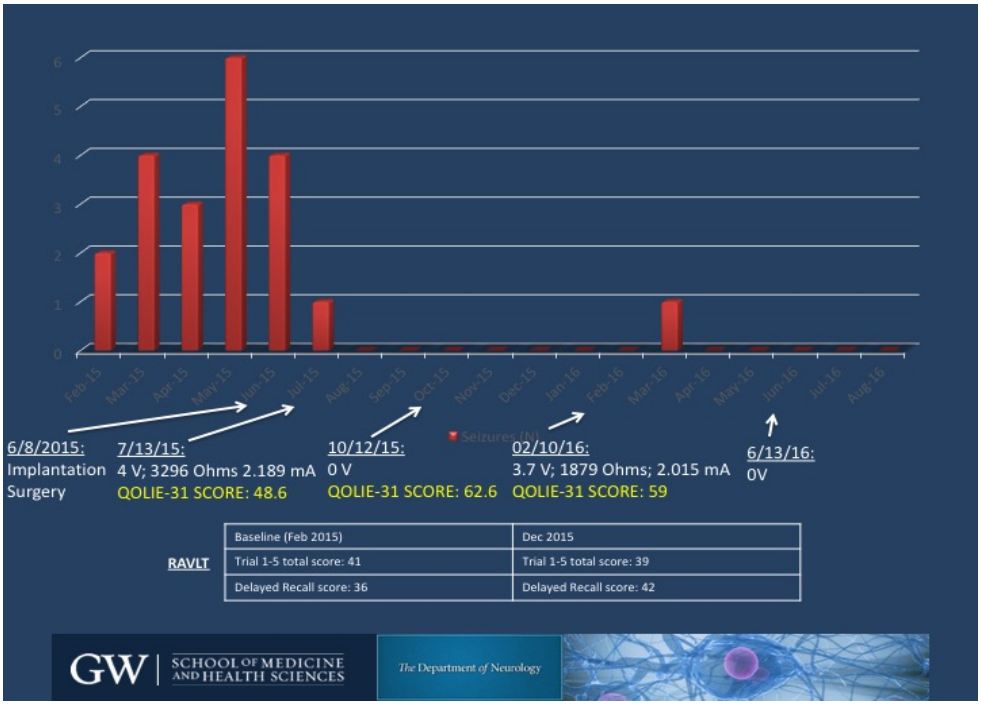

Figure 4: Subject 102 baseline and follow-up seizure frequency, QOLIE-31 and RAVLT scores

Potential Adverse Events

The general DBS procedures and potential adverse events are the same for all targets in the brain. The two most common applications of DBS are for essential tremor and movement disorders. DBS for essential tremor was approved by FDA in 1997 and DBS for Parkinson's disease in 2002. A summary of the adverse events that occurred in the prospective trials used to support the indications of Parkinson's disease and essential tremor is provided. The summary is limited to adverse events that would be expected with DBS in general.

The conclusions drawn from Parkinson's studies in 160 patients with 289 DBS implants was that the preclinical and clinical testing provided reasonable assurance that the Activa Parkinson's Control System is safe and effective when used in accordance with its labeling. The conclusions from the essential tremor DBS study involving 424 patients with 464 DBS implants (Activa Tremor Control System) was that the DBS system was well tolerated by the participants with a safety profile that was similar to the approved indication for Parkinson's disease. We expect less adverse effects in the proposed trial since the intended DBS frequencies are low (1 or 5 Hz) as opposed to the high frequencies used in movement disorders.

Research Design and Methods

PART II: INVESTIGATIONAL PLAN

Purpose

Low frequency stimulation is an attractive, uninvestigated method for treatment of intractable epilepsy. Preliminary animal and human data suggest safety and remarkable efficacy of LFS in epilepsy. In addition, the duty cycle of LFS is very low, implying less electric current injection, with less charge density on the target tissue and electrodes, and longer battery life. The current project is a classic translational, single blinded, randomized research project, demonstrating a clear path from the laboratory to bedside. If successful, this new therapy will be of great value to patients with medically intractable MTLE.

The primary aim of the current proposal is to evaluate safety and tolerability, in terms of neuropsychological effects, of low frequency electrical stimulation of the fornix (LFSF) in participants with medically-intractable MTLE. Secondary aims include evaluation of psychiatric changes, seizure frequency, and quality of life during LFSF.

The study will:

- Develop a multidisciplinary clinical research protocol to be conducted at The George Washington University, Washington, DC to evaluate the safety and tolerability of low frequency electrical stimulation for treatment of intractable Mesial Temporal Lobe Epilepsy (MTLE)
- Enroll up to 16 participants over one site into a single-blinded study to evaluate the safety and tolerability of low frequency electrical stimulation of the fornix ipsilateral to the epileptic hippocampus.

The secondary outcome measures will include:

1. To standardize the implantation, hippocampal evoked potential recording, and current determination procedures in preparation for the next protocol phase
2. Assess the effects of LFSF on psychiatric symptoms using standardized measures
3. Evaluate seizure reduction by total percentage of seizure frequency changes, changes in secondarily generalized seizure frequency, and changes in seizure free days

4. Assess overall quality of life

Protocol Overview and Design

Participation Criteria

The protocol expects to enroll and follow up to 16 participants at The George Washington University throughout the course of the study. Study participants will be persons of any race, ethnic group, or gender who experience intractable mesial temporal lobe epilepsy. Participants who enter will be able to withdraw from the study at any time without affecting their access to other treatments at The George Washington University or its affiliated hospitals. The first 20 eligible and consenting participants will be accepted into this study. No gender or minority will be excluded. However, since the sample size is small and consecutive participants will be accepted there may be an inadequate representation of ethnicities, genders, and race in the study sample.

The study is expected to last approximately five years, from enrollment of the first patient to completion of the final subject, taking into consideration attrition and otherwise-eligible subjects who will not elect to participate. Once the study is completed, and enrolled participants have completed all required elements of the protocol, a final report will be submitted to the FDA. Participants may also discontinue their participation in the study if they wish at any time.

At the request of the participant, DBS systems can/will be removed, or stimulation settings on the DBS system can be turned off as to return the participant to their baseline status before their participation in the trial. Participants may also be terminated from the study if lost to follow up or at the discretion of the physician.

Inclusion and Exclusion Criteria

Inclusion Criteria:

- Participants are between the ages of 18 - 65 years of age
- Participants must have had a non-invasive video-EEG monitoring revealing seizure semiology and ictal EEG consistent with unilateral or bilateral MTLE
- Participants must have tried and failed two trials of antiepileptic drugs (AEDs)

- Participants may have lesional or non lesional hippocampi, as evidenced by brain MRI acquired within the previous two years.
- Participants are prescribed and taking 1-4 AEDs at the time of study entry
- Study participants will have intractable MTLE with a seizure frequency of at least 1/month averaged over the preceding 6 months prior to enrollment, including maximum seizure-freedom periods of no more than 60 days.
- Participants must have a platelet count greater than 125,000 per cubic millimeter and prothrombin time (PT) and activated partial thromboplastin time (aPTT) within normal limits at the visit prior to surgery

Exclusion Criteria:

- Progressive neurological or medical diseases, such as brain tumors or neurodegenerative disease or cancer.
- Non-compliance with antiepileptic medications as demonstrated by the medical record
- Any conditions interfering with electrode implantation
- Any non-epileptic seizures.
- Inability or unwillingness to complete neuropsychological tests or complete seizure diaries.
- Current drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements.
- Pregnant, or planning to become pregnant*
- Participation in another research trial where the participant was treated with another investigational drug or device within 30 days prior to enrollment of study.
- IQ showing a General Ability Quotient of less than 70. The score excludes the contribution of working memory and processing speed (which are areas of cognitive functioning that are vulnerable to numerous influences including seizures and fatigue and effects of AEDs).
- Inability or unwillingness of individual or legal guardian/representative to give written informed consent.
- Participants who have changes to their antiepileptic medications during the baseline phase (as they will need to repeat the baseline phase).
- Subjects with history of status epilepticus within the preceding year.

- History of psychiatric illness necessitating hospitalizations.
- Subjects who have any of the following implanted devices: aneurysm clips, cardiac pacemaker or defibrillator, cochlear implant, spinal cord, DBS, or vagal nerve stimulator.
- Co-morbid conditions that would interfere with study stimulation activities or response to treatment, which may include:
    - Neoplasm with life expectancy < 5 years
    - Severe chronic pulmonary disease
    - Local, systemic acute or chronic infectious illness
    - Life threatening cardiac arrhythmias
    - Severe collagen vascular disorder
    - Kidney failure or other major organ system failures

Risk to Pregnancy:

Women who are pregnant cannot take part in the study. Women who become pregnant during the study may be withdrawn from the study and will continue with standard clinical care as indicated. If participants are female and become pregnant or are pregnant there may be risk to them or to the embryo or fetus.

Informed Consent

Before any screening procedure is performed, a signed informed consent will be obtained from each participant. The informed consent form will incorporate Health Insurance Portability and Accountability Act (HIPAA)-compliant wording, by which participants authorize the use and disclosure of their Protected Health Information (PHI) by the investigator and by those persons associated with the research for the purposes of this study.

The details of research study purpose and design will be explained verbally to the potential participant by the principle investigator or another qualified member of the research team. A written informed consent form will be given to the participant in order to be read and understood, and the participant will be given sufficient time to thoroughly read and review the document. The participant will be encouraged to take the informed consent document home to discuss with family members or medical care providers. Each participant will be given ample opportunity to inquire

about details of the study with members of the research team and to read and understand the consent form before signing it.

Consent will be documented by obtaining a dated signature from the participant. A participant may not be admitted to the study unless informed consent of the participant has been obtained. A copy of the signed informed consent document will be provided to the participant to keep for their records upon completion.

Each participant's signed informed consent document will be kept on file by the Principal Investigator/research team for possible inspection by regulatory authorities.

Only qualified investigators and members of the research team associated with the protocol, who are certified in Human subjects Protections according to the local IRB's policies and procedures, will obtain consent from all participants. Informed consent will be obtained from all participants who meet the inclusion criteria. Individuals will only be included if they have the ability to provide informed consent.

All participants are expected to be able to complete the informed process and provide their own written signature on the document. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy will be given to each participant and this fact will be documented in the participant's record.

The intent is not to specifically target illiterate or non-English speaking individual. However, as these individuals may very well be part of the recruitment pool and may have the ability to provide informed consent, the study team will have provisions for including these individuals if eligible for participation.

Provisions for inclusion of illiterate individuals: The Informed Consent Form will be read to the illiterate participants in the physical presence of a non-study staff third party witness, who would then sign the consent acknowledging that the participant was informed about participating in the research and agreed to participate. Any individual who does not appear to fully understand the purpose of the study will be excluded.

Provisions for inclusion of non-English speaking individuals: Participants who do not speak English will be given an informed consent document written in a language understandable to them. Translated consent documents for populations that are non-English speaking will be submitted to the IRB for review and approval. The principal investigator will provide the qualifications of the individual or the service that was used to translate the informed consent documents.

When informed consent is obtained from non-English speaking participants using a translated consent form all the following will be done: A translator who is fluent in both English and the language of the participant will be present if the person obtaining consent does not speak the language of the participant.

The consent document will be signed and dated by the participant. The consent document will be signed and dated by the person obtaining consent and/or, if the person obtaining consent does not speak the participant's language, by the translator.

Participant Privacy: Participant will not be identified (by name, street address, social security number, etc.) in any manner outside of The George Washington University. If the study results are published, no information will be included that can identify participants. All participant interactions will take place in a private area with only study staff present.

Study Phases

The study design will consist of the following five (5) phases listed below. It is important to note that the underlined steps will have already been completed as part of the standard, routine clinical care, rather than for research. Confirmation that the underlined items listed below have been completed will be done during an evaluation of the participant's case history and medical record:

I. Recruitment and Enrollment Phase

a. Review of participant case history and medical record for verification of the following:

i. Completion of seizure protocol brain MRI

ii. FDG-PET Scan if needed to optimize placement of intracranial electrodes as determined by the site PI and their epilepsy teams.

iii. Neuropsychological Testing

iv. Ictal Recording during Video EEG Monitoring

b. Verification of inclusion/excision criteria

c. Signing of Informed Consent Document

II. Baseline Phase (Approximately 3 Months)

a. Assessment of Baseline Seizure Frequency with Completion of Seizure Calendar

b. Neuropsychological Testing (if I.a.iii, above, did not include such key tests as RAVLT)

c. Psychiatric Testing

d. Quality of Life Evaluation (QOLIE-31) Questionnaire

III. Depth Electrode/DBS Electrode Implantation and Recovery Phase ***(****It is important to note that the underlined steps will be completed as part of the standard, routine clinical care, rather than for research)*

a. Implantation of diagnostic depth electrodes

b. Implantation of the DBS lead

c. Evaluation in Epilepsy Monitoring Unit (Approximately 5-10 days)

i. Confirmation of hippocampal seizure onset

ii. Removal of depth electrodes

iii. Connection of forniceal leads subcutaneously to implantable pulse generators

IV. Randomization and Blinded Stimulation Phase (Approximately 12 months)

a. Randomization of participants to a stimulation group of either 1 Hz or 5 Hz (see Fig. 1)

b. Neuropsychological Testing

c. Psychiatric Testing

d. Quality of Life Evaluation Questionnaire

e. Assessment of Seizure Frequency with Completion of Seizure Calendar

f. Adverse Event Assessment

V. Long Term Follow up Phase (Approximately 12 months)

a. Quality of Life Evaluation Questionnaire

b. Assessment of Seizure Frequency with Completion of Seizure Calendar

c. Adverse Event Assessment

Phase I: Recruitment and Enrollment

Potential surgical candidates are reviewed on a weekly basis during a multidisciplinary epilepsy management conference at The George Washington University. Participants will be chosen as potential candidates by the principal investigator, Dr. Mohamad Koubeissi, during this patient care conference at The George Washington University.

Routine care of patients with intractable epilepsy includes referral to the Epilepsy Monitoring Unit (EMU) for characterization and localization of seizures. Medically-intractable patients are then presented at the weekly multidisciplinary Epilepsy Surgery Conference, attended by all epileptologists and epilepsy surgeons. For the proposed research protocol, we expect to recruit up to 16 participants at one site over the course three years (see power analysis). However, the total length of the study, from the enrollment of the first participant to the conclusion of procedures for the final participant will span approximately 5 years. Thus, each subject follow up is expected to be one year, but the whole study (recruiting 16 subjects) will be expected to take 5 years.

The presurgical evaluation will be carried out according to routine clinical practice. The following is a list of evaluations that are necessary to assess whether an individual meets enrollment criteria. Again, it is important to note that the underlined steps will have already been completed as part of the standard, routine clinical care, rather than for research:

- Video-EEG monitoring with scalp electrodes, with the recorded seizures and interictal epileptiform discharges suggesting MTLE
- MRI showing lesional or intact-looking hippocampus on the seizure-onset side

- Neuropsychological Testing suggesting intact memory function
- Quality of Life in Epilepsy 31 (QoLIE-31)
- Seizure frequency of 1/month to 10/day as demonstrated by a seizure diary averaged over 6 months with no seizure-freedom period lasting longer than 60 days.

Enrollment is defined as the day the individual has met all the screening criteria and signed the Informed Consent form. Study participants will have intractable unilateral or bilateral MTLE.

Phase II: Baseline Phase:

Enrolled participants will then enter into the baseline phase prior to implantation; this phase will last for approximately two months. Participants will be given a seizure calendar and specific written and verbal instructions on how to complete the calendar in order to properly assess their seizure frequency, prior to implantation.

Participants will complete their calendars accordingly and will submit to a member of the research team for review by a study physician prior to implantation. Participants will also undergo the following during the baseline phase:

- Neuropsychological testing (if not performed in Phase 1)
- Psychiatric testing
- Quality of life in Epilesy-31 Assessment
- Concomitant Medication Assessment

These items will be reviewed by the study physician and other qualified research personnel prior to implantation to ensure that the participant remains qualified to proceed with the remaining phases of the protocol.

Phase III: Implantation

On the day of the implantation procedure, participants will have standard blood laboratory testing completed. These blood testing procedures are part of the routine care process and are considered standard of care for all surgical candidates.

Intervention, Administration, and Duration:

As per routine clinical care, the invasive evaluation of participants with non-lesional MTLE aims at confirming the seizure-onset zone in the hippocampus. All participants will have undergone video-EEG monitoring with scalp electrodes, with the recorded seizures and interictal epileptiform discharges suggesting MTLE. Since these participants have non-lesional or lesional hippocampi, depth electrode implantation will aim at investigating whether the seizure onset zone is indeed in the hippocampus versus other clinically silent cortical regions with secondary propagation to the mesial temporal lobe.

The stimulating electrodes will be implanted unilaterally in the fornix during the same clinically-indicated surgery for depth electrode implantation. Only one depth electrode with multiple contacts will be implanted in the fornix unilaterally. If recorded seizures in the Epilepsy Monitoring Unit (EMU) show onset in the hippocampus, the forniceal leads will be connected subcutaneously to subclavicular stimulators. Thus, there will be only one lead and one implantable pulse generator per patient.

Thus, implanted regions will include, in addition to the amygdala and hippocampus, areas with known connectivity with the hippocampus, such as the posterior cingulate gyrus, basal frontal cortex, insula, temporal neocortex, and the temporo-occipital junction.

In all participants, Leksell frames will be placed and brain MRIs obtained in the frame. The images will be exported to a computer that aids in digital planning of electrode implantation (e.g. the iPlan workstation - Brainlab, Inc. Westchester, IL, USA). Participants will be brought to the operating room and the areas of the intended incisions clipped and draped in a sterile manner for each electrode. A twist drill used to make a small hole through which electrodes will be advanced to target regions under fluoroscopic guidance and secured with an anchor bolt.

Monitoring depth electrodes will be ones used routinely for monitoring (e.g. platinum-iridium cylinders measuring 1.1 mm in diameter and 2.3 mm in length, evenly spaced at 5 mm intervals -

Adtech, Racine, WI, USA). Each depth electrode probe contains a number of contacts, often 12, facilitating recordings from both deep and superficial cortical areas. During this same *clinically-indicated* surgery, Medtronic Model 3389DBS leads (Medtronic, Minneapolis, MN, U.S.A.) will be introduced into the fornix by a rigid introducer hooked to a wire loop at the tip. These leads comprise four contacts at the implanted tip, 1.5 mm long and spaced 0.5mm apart (Figure 5). Only two of these four contacts will be selected for connection to the pulse generator.

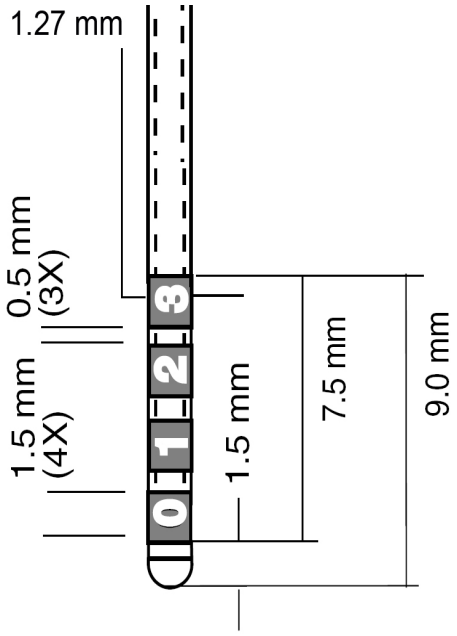

Figure 5: Model 3389 DBS leads have narrow (0.5 mm) spacing between each of the four electrodes at the distal end, providing electrodes spread over 7.5 mm.

	Prior to enrollment		**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Long Term Follow Up**
		Baseline Phase (3 months)	Implantation and Recovery	Month 1	Month 3	Month 5	Month 7	Month 9	Month 11	Month 13	Months 14-25
Procedures											
Seizure Protocol Brain MRI	X										
FDG PET Scan	X										
Neuropsychological Testing	X					X		X		X	
Intracarotid Amobarbital Procedure (IAP)	X										

Video EEG Monitoring	X										
Eligibility Criteria	X										
Informed Consent	X										
Medical History	X										
Seizure Calendar		X		X	X	X	X	X	X	X	X
Psychiatric Testing		X				X		X		X	
Quality of Life in Epilepsy-31 Questionnaire		X		X	X	X	X	X	X	X	X
AE Review			X	X	X	X	X	X	X	X	X
Electrode Implantation			X								
Epilepsy Monitoring Unit (5-10 days)			X								
Randomization				X							
Device Interrogation and Programming				X	X	X	X	X	X	X	

Figure 6: Study flowchart

Stimulation Parameters:

For safety purposes, we will ensure that charge density does not exceed Q_{max}= 30μC/cm^2, which is the maximum charge density that is considered safe by FDA(Kuncel and Grill 2004). For the proposed project, we will be using Model 3389 DBS leads (Figure 5), which are shaped like a cylinder with a length of 1.5 mm and diameter of 1.5 mm with an inter-electrode distance of 0.5 mm. This model allows similar settings and inter-electrode distance to those used in our preliminary studies (if electrodes 0 and 3 are chosen), but will also allow wider activation, if the need emerges to optimize hippocampal evoked responses.

Wider activation can be achieved if two continuous electrodes are stimulated and a third electrode is chosen as a reference. For the intended lead model, the surface area in contact with brain tissue is A = 2π (0.15/2) x 0.15 = 0.07cm^2. If total biphasic pulse duration is 0.2msec, then phase duration is 0.1msec. Q_{max}/area = 30 x 10^{-6} C/cm^2 = (0.1 x 10^{-3} sec) x I (A)/ 0.07 cm^2, yielding a maximum safe current of I = 21 mA. Thus, the maximum intended current of 8 mA/phase is a safe current.

Handling of Study Interventions:

Intra-operative X-rays will be obtained, and temporary percutaneous leads will be left externalized during the EMU stay to allow verification of electrode integrity and selection of the two leads for permanent connection. Electrode integrity will be tested by the hand-held portable stimulator connected pair-wise to the external ends of depth brain lead contacts. Since DBS generators are mostly voltage sources, and those that are current sources do not deliver pulses at frequencies of less than 30 Hz, a Medtronic device can be used to estimate impedance and facilitate converting the intended 2, 4, or 8 mA into equivalent voltage to be delivered at low frequencies.

In the operating room, stimulation for testing electrodes will be delivered as 0.2-ms square wave pulses, with negative polarity connected to the deeper contact for consistency (2 Hz, voltage equivalent to 2-8 mA, for 50 sec) and the evoked responses will be recorded in the hippocampus. If no evoked potentials are recorded, then the location of the forniceal electrode will be adjusted under X-ray guidance until hippocampal evoked potentials are elicited. A head CT scan will be obtained post-operatively and the locations of the depth electrodes will be verified by co-registration of pre-surgical volumetric brain MRI with post-surgical volumetric brain CT (e.g. using Brainlab, Inc. Westchester, IL, USA).

The patient will then be transferred to the EMU where Electrocorticographic (ECoG) recordings will take place. ECoG channels will be amplified, filtered (0.1-300 Hz), and recorded digitally with a sampling frequency of 1-10 kHz. Monitoring will normally take 5-10 days during which anti-epileptic medication dosages will be lowered in order to increase chances of ictal recordings. If hippocampal seizure onset is established, then the patient will be taken back to the operating theater where all depth electrodes will be removed, except the fornix electrode, whose percutaneous wires will be cut and discarded. Permanent sterile leads will be connected subcutaneously to a Medtronic Activa SC Model 37602 Neurostimulator on the anterior chest wall in the infraclavicular fossa.

The Activa SC Model 37602 is a multi-program device that delivers stimulation through one lead. The stimulation settings are stored in programs consisting of a specific combination of pulse width, rate, and amplitude settings acting on a specific electrode combination. This device is commercially available investigational device for DBS. Its power source is 4.5 Amp hours, hybrid combined silver vanadium oxide cell with nominal voltage of 3.2 V.

Phase IV: Randomization and Blinded Stimulation Phase

One month following the implantation phase, participants will return to the hospital and will be randomized into a stimulation group where their stimulation parameter settings will be placed at either 5Hz or 2 Hz by a qualified member of the research staff. During the course of this phase, participants will be instructed to continue with the completion of their seizure calendars.

Once a participant has been randomized, they will proceed into a treatment stimulation block which will last approximately 2 months. The participant will be blinded to the frequency setting of their DBS system, to either 2 Hz or 5 Hz, and to the intensity setting of their system to 0, 2, 4, or 8 mA.

Participants will complete one block of stimulation (2 months), and then proceed into a non-treatment block for a washout of a carryover effect (i.e., where all settings will be placed at 0) for approximately 2 months. In full, participants will cycle through 6 alternating blocks, 3 treatment stimulation and 3 non-treatments (Figure 7). During the treatment stimulation blocks, stimulation will be delivered 4 hours on, 4 hours off on a 24 hour cycle. In the event that a participant experiences ≥ 90% seizure reduction in first three months, they will remain at 2 mA and no increase to frequency setting will take place.

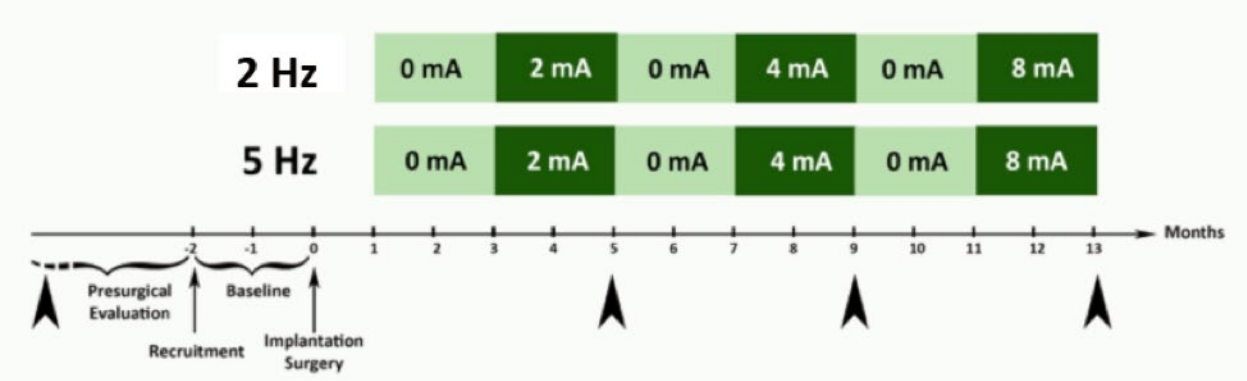

Figure 7: An overview of the study design. According to standard clinical practice, the presurgical evaluation will include a seizure-protocol brain MRI, a brain FDG-PET scan, neuropsychological testing, Intracarotid Amobarbital Procedure (IAP), and ictal recordings during video-EEG monitoring with scalp electrodes. An ictal SPECT scan is also done in some patients. Patients with presumable MTLE and normal brain MRI will be recruited. Seizure calendars will be given and baseline seizure frequency assessed for two months before implantation surgery. The patients will be monitored in the Epilepsy Monitoring Unit (EMU) for approximately 1 week, and if hippocampal seizure onset is confirmed, a pulse generator will be implanted and connected to the forniceal lead. Randomization will occur one month later into 2 Hz or 5 Hz groups. The patients will be blinded to the frequency (f = 2 Hz vs. 5 Hz) and to the current intensity (I = 0, 2, 4, or 8 mA). Every treatment block (I > 0 mA) will be followed by a no-treatment block (I = 0 mA) for washout of carry over effect. All DBS will use a 4-hours-on, 4-hours-off

schedule. Arrowheads indicate times for neuropsychological testing. Anti-epileptic medication regimens will not be changed for the duration of the study.

Participants will return for research related follow up visits at the following time points:

- Month 1 (post-implantation)
- Month 3
- Month 5
- Month 7
- Month 9
- Month 11
- Month 13

During the research related visits at the above time points, participants will undergo the following procedures/tests:

- Adverse Event Evaluation(every visit)
- Neuropsychological Testing (prior to enrollment and at months 5, 9, and 13)
- Device Interrogation and programming (every visit)
- Review of Seizure Calendars (every visit)
- Psychiatric Evaluation (at baseline, months 5, 9, and 13)

Phase V: Long Term Follow up Phase

Participants will be evaluated on a long term basis, where they will no longer be blinded to their stimulation settings. Stimulation parameters can be adjusted by a member of the research team as clinically indicated. Participants in the long term follow up phase will be contacted monthly via telephone by a member of the research team to discuss any adverse events that may have occurred, any issues pertaining to the implanted stimulation system, any seizures and the participants' overall quality of life while at home.

Neuropsychological Tests

The primary outcome is safety and tolerability of LFSF in participants with intractable MTLE as regards memory function.

Stimulation of the fornix has been found to improve memory function in patients with Alzheimer's disease (Laxton, Tang-Wai et al. 2010). These authors implanted DBS leads in the anterior fornix and hypothalamus, and source imaging demonstrated that stimulation activated regions that are part of Papez circuit. Our preliminary data confirm these findings with much stronger evidence than source imaging: direct intracranial recordings confirmed short-latency evoked potentials in the hippocampus, and longer-latency ones in the posterior cingulate gyrus (Fig. 2). Further, we have found a slightly higher mental-status examination score during LFSF. In the planned project, more detailed neuropsychological testing will be done.

Memory functioning will be measured using the Rey Auditory-Verbal Learning Test (RAVLT)(Rey 1964). In this test, the examiner reads a 15-item word list at a fixed rate and requires the examinees to repeat as many words as they can remember after each presentation; the list is presented 5 times (Trials 1-5), and the sum of the 5 trials provides a sensitive index of efficiency of acquisition. Recall is tested again after the examinee is required to repeat a distraction list (List B) and again 30 minutes later (Delayed Free Recall), followed immediately by a Recognition Trial (discriminating the original 15 targets from 50 distractors).

Verbal learning tests have been used extensively to measure adverse changes following left and right temporal resection for medically refractory TLE, and the RAVLT has been shown to be more sensitive than its counterpart, the California Verbal Learning Test (Loring, Strauss et al. 2008). Furthermore, repeated RAVLT testing has been shown to be resistant to retest effects in clinical trial paradigms, even when repeated one week apart over 6 consecutive weeks (Fastenau, Hankins et al. 2001; Fastenau, Hankins et al. 2002; Beglinger, Ahmed et al. 2003; Beglinger, Gaydos et al. 2005).

All participants will complete the forms in sequence (beginning with Form 1 and continuing through Form 6) across 6 data collection points (pre-stimulation baseline and at the end of each 2-month treatment block). The specific outcome variables will be RAVLT Sum of Trials 1-5 and

Delayed Recall and Delayed Recognition Percent Accuracy. These will be analyzed as continuous variables. In addition, each patient in the clinical trial will be classified according to whether or not they have shown clinically significant change beyond what could be expected by practice or chance alone.

To achieve this, the scores of historical controls with medically refractory left TLE but who have not undergone surgery or DBS will be compared over the same intervals to generate test-retest reliability coefficients for computing reliable change indices corrected for practice (RCI-p) using a method developed in part by Dr. Hans Lüders, (Chelune, Naugle et al. 1993), which has been shown to be among the most accurate methods for quantifying individual change on neuropsychological tests (Temkin, Heaton et al. 1999).

Endpoints and Outcomes:

Primary Outcome:

The primary outcome is safety and tolerability of LFSF in participants with intractable MTLE as regards memory function.

Secondary Outcomes:

PSYCHIATRIC HEALTH: Since LFSF is expected to activate limbic structures, we will assess the effects of LFS on psychiatric symptoms using standardized measures that are known to be sensitive to changes to surgical treatment of TLE. Primary psychiatric outcome will be evaluated with the rater-administered Brief Psychiatric Rating Scale (BPRS)(Overall and Gorham 1962), which has been used to assess global psychopathology in mood, anxiety and psychotic disorders related to TLE (Glosser, Zwil et al. 2000). The BPRS will be complemented with the Hamilton Depression and Anxiety Scales, as well as the Modified Scale for Suicidal Ideation.

Electrode implantation in the fornix is technically feasible. We have successfully implanted depth electrodes in the fornix in 7 patients, stimulated them, and recorded evoked potentials from the hippocampus. For the proposed project, we plan to implant Model 3389 DBS leads using the same technique of stereotactic implantation. These leads are inserted routinely for DBS in patients with Parkinson's disease. A secondary aim of this trial is to standardize the implantation, the evoked

potential and electric current determination procedures in preparation for a large-scale phase III trial.

EFFECT ON SEIZURE FREQUENCY: We expect LFSF to result in seizure reduction based on our preliminary data and a number of studies (Yamamoto, Ikeda et al. 2002; Albensi, Ata et al. 2004; Goodman, Berger et al. 2005; Schrader, Stern et al. 2006; Kile, Tian et al. 2010) For outcome measures, we will use (1) total percentage of seizure frequency change, (2) change in secondarily generalized seizure frequency, and (3) change in seizure-free days.

QUALITY OF LIFE: We will use QOLIE 31 to assess quality of life.

Documentation of Reasons for Ineligibility and Non-Participation

All participants will undergo a screening examination of their medical records to evaluate their clinical condition. The screening evaluation will take place either before admission for a planned diagnostic evaluation, or during the admission for a patient who is already admitted for workup or treatment. All patients who will be screened for this study will be logged into the Case Report Form (CRF) Screening Log. If a patient is deemed ineligible, then the reason for exclusion will be documented.

Early Termination/Withdraw from Study:

Participants who discontinue study intervention early will be asked to return to the study site for a final follow-up visit. The PI will perform a final physical and check for adverse events. The coordinator will collect any information related to monitoring and reporting of adverse experiences for follow-up on participants once they have notified the study staff or PI in writing of discontinuation.

Risks and Side Effects:

Risk Analysis

Risks

The general risks associated with DBS for temporal lobe epilepsy are expected to be similar to some of the adverse events of DBS trials involving FDA approved applications for Parkinson's disease, dystonia, essential tremor and OCD. In addition, the risk profile may also be similar to chronic pain, Tourette's, and major depression. The potential risks for any DBS procedure are divided into three categories. These risk categories include those associated with surgical implantation of the DBS lead and pulse generator, risks associated with the implanted device, and risks associated with the programming of the device.

General surgical risks associated with DBS implantation include hemorrhage, paralysis, coma and or death, stroke, seizures, infection, allergic reaction, leaking of fluid surrounding the brain, temporary and or permanent neurological complications, pain at the surgery sites, and headaches.

The risks associated with implanted devices include those which are mechanical, electrical, software, and others related to device system failure. Other risks include battery failure, electrical shock, and reactions to the various components of the device. The lead extension or lead may shift/move after being implanted in the body, which would require a surgical intervention to adjust.

Side effects which are related to stimulation are most commonly reversible by adjusting the stimulation parameters or by reprogramming the stimulation settings. In addition to reprogramming, the system can also be turned OFF, with the intensity placed at 0 V, and the patient will return to their baseline state. A recent summary of the risks profile for DBS in movement disorders included suicidal ideation, depression, gastrointestinal disturbances, nausea, muscle weakness (partial paralysis), jolting or shocking sensation, numbness, paresthesia, facial flushing, motor contraction, dizziness, changes in vital signs, hyperactivity or euphoria, pain or discomfort, headache pain, restlessness, weight gain or loss, speech and visual difficulties, blurred or double vision, changes in energy levels, mood changes, unusual taste or smell sensations, and cognitive and or behavioral changes.

The profile of potential adverse events associated with using DBS as a therapeutic option are well defined, therefore any change in the clinical status of a patient during the course of the research trial is likely to be detected early by one or more physicians. In addition, these clinical events will be screened for and monitored during the follow-up research visits.

Serious Adverse Events

A serious adverse event (SAE) is any undesirable experience or untoward medical occurrence associated with the use of a medical product (Title 21 CFR Part 312) that:

- Leads to death
- Leads to one of the following:
    - Life threatening illness or injury
    - Required inpatient hospitalization or prolongation of existing hospitalization
    - A permanent impairment of a body structure or a body function
    - Medical or surgical procedure to prevent permanent impairment or damage to a body structure or function

Unanticipated Adverse Device Effects

An adverse device effect (ADE) is any serious adverse effect on the health or safety or any life threatening problem or death caused by, or associated with the device or stimulation therapy if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in to application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants (21 CFR 812.3):

- The implanted components (lead, extension, neurostimualtor)
- The lead/extension tract or neurostimualtor pocket
- The burr hole site

An event will ***not*** be considered related to the device when it is the result of:

- A preexisting medical condition
- A medication

Device Malfunction

A device malfunction is a failure of a device to meet its performance specifications or other performance as intended. Performance specifications include all claims made in the labeling for

the devices. The intended performance of a device refers to the intended use for which the device is labeled or marketed (21 CFR 803.3)

Documentation of Adverse Events

All AE's from the time the study informed consent is signed through the final study visit will be recorded an AE's on the study event log; each event being documented separately. All AE's and SAE's will be followed until:

- AE is resolved and has returned to normal/baseline or has stabilized
- Participant has withdrawn from the study
- AE is judged by the investigator to be no longer clinically significant
- Study closure

Dr. Koubeissi will serve as the Point of Contact to which the team will report all adverse events at GW. All SAEs from GW will be reported to the GW IRB within 5 business days. The sponsor will ensure that all non-serious adverse events will be reported to the FDA and to the respective Center Institutional Review Board (IRB) during the annual reporting period at George Washington University.

All adverse events, which include serious adverse events, will be categorized as follows:

- **Surgical/Procedure-Related**: Associated with surgical implantation of the depth electrodes and Deep Brain Stimulation system
- **Device Related**: caused by the implanted systems
- **Therapy Related**: caused by the electrical stimulation of the nervous system while treating the participants symptoms
- **Disorder Related**: an event that might reasonably be attributed to the participants underlying disease state,

For those events that are determined to be related to stimulation therapy or device specific, the sponsor/investigator will report the strength of the relatedness using the following terms:

- **Definite:** The event is resolved with reprogramming of the stimulation parameters and is confirmed by the reappearance of the event with the device settings are returned to the settings programmed at the time the event was observed

- **Probable**: The event resolves upon reprogramming of the stimulation parameters and cannot be reasonable explained by the participants current clinical state

- **Possible**: The event may have been produced by the study participant's clinical state, however, the effect of stimulation cannot be ruled out

Reporting of Serious Adverse Events

Serious adverse events (SAE), including all death, both at GW and all participating sites must be reported to the GW IRB within 5 business days after the investigator first learns of the event and in accordance with the IRB SAE reporting requirements at George Washington University. Investigators should attempt to determine, whether the SAE is related to the stimulation system or the therapy.

The sponsor will report the available information on all SAE's to the FDA within 10 working days of learning of the event. Any SAE, which occurs during the study, whether or not related to the stimulation system, will also be reported to the Data Safety Monitoring Board.

Procedures for Minimizing Risks

Investigators chosen to be a part of this protocol have a great deal of expertise with the management of epileptic patients and also with DBS. The various inclusion/exclusion put forth in the research protocol have been designed to select only those participants who will most likely benefit from this study as well as excluding those with higher risks. Study participants will be closely monitored after the implantation of the stimulation system by neurological and epilepsy specialist. In addition, study participants will be monitored in units that are staffed specifically with personnel who are experienced and equipped to care for the complex nature of each participant's neurological status.

If during titration, symptoms develop that affect the participant safety or the participant quality of life, stimulation parameters will be immediately adjusted. If the adjustment does not relieve the problem, and the participant's symptoms persist, stimulation will be discontinued.

Participants may also terminate from the study if they wish at any time. Those who also enroll in the research study may also wish to discontinue (turn OFF) their stimulation for any reason. DBS systems will also be surgically removed if the research participant asks for removal. In addition, research participants who prematurely withdraw or removed from the research study due to the occurrence of an adverse event will be followed (e.g., telephone contact, and/or follow-up visits, etc.) until resolution of the event occurs.

Monitoring Plan and Description

The data management for this study will maintain a level of data integrity and confidentiality that will provide optimum adherence to all 21 CFR regulations, while providing a standardized method of data collection and recording to enable the investigators, sponsors and regulatory agencies to accurately reconstruct the events of the study, confirm the compliance of the protocol, and produce accurate data that is appropriate in demonstrating study results.

Research staff and study coordinators at George Washington University will perform primary data collection based on source documents from the hospital charts. Paper case report forms (CRF's) will be used to collect study data. Study coordinators/research staff will complete all appropriate sections of the CRF's. The study sponsor/PI and site PI will review the information documented in the CRF's and verify the information recorded is consistent with medical records and other source documents. Study research staff will correct all identified errors or incomplete entries on the CRF's. Final CRF's will be reviewed and signed by the principal investigator.

Per FDA Code of Federal Regulation, part 812.46, the principal investigator will monitor and ensure that the co-investigators at George Washington University are conducting all research related activities in compliance with their institutional rules and regulations, in addition to adhering to the approved research protocol.

All research related information from the second site will be relayed to the principal investigator on a per participant enrollment status; in addition to all screening and enrollment logs and adverse event information.

Investigator Training

The principal investigator will ensure that all research related personnel at George Washington University have been adequately trained on the approved protocol, approved informed consent, and are familiar with all research related activities being conducted during the course of the protocol before the enrollment of the first participant.

All members who have been adequately trained can then have tasks appropriately delegated to them by the principal investigator in accordance with their credentialing, and licensure. Research related personnel and their delegated research duties at George Washington University will be recorded on a log and kept current throughout the course of the research trial. It is the overall responsibility of the principal investigator to ensure compliance and participant safety throughout the course of the research trial.

Data Safety Monitoring Board

A data safety monitoring board (DSMB) will be established by the sponsor to evaluate the data obtained during the course of this trial (21 CFR 812.46). Members of the clinical trial DSMB, who will have specific background expertise in their medical and/or scientific field, will be chosen as members.

Members of the board can advise the sponsor and make recommendations on the continuing safety of enrolled participants, as well as the continuation of validity and scientific soundness of the ongoing research trial. The members will function in their capacity under the approved charter; this charter will also be submitted, reviewed, and approved by George Washington University Institutional Review Board. Corresponding minutes and recommendations made to the sponsor by the DSMB will be submitted to the Food and Drug Administration and local intuitional review board during the time of annual review.

Regulation and Ethical Conduct of the Research Study

The study will be conducted according to the clinical investigational plan submitted, by the laws and regulations of the United States Food and Drug Administration, parts 50, 54, 56, and 812 of the FDA CRF.

In addition, all investigators associated with the trial will conduct all procedures in accordance with their signed investigational agreement.

Benefits:

Potential Benefits

Low Frequency Stimulation of the Fornix (LFSF) aims to reduce seizures in patients with intractable mesial temporal lobe epilepsy (MTLE), thus offering an additional therapeutic option besides resective surgery, which is irreversible. .

Study Justification

The study is justified by the lack of therapeutic options that patients with medically-intractable MTLE have. In addition, Low frequency stimulation has been shown to be safe and effective in animals and in our preliminary data in humans, justifying the translation into a clinical trial.

Costs to Subjects:

There are no costs to subjects for participating in this study,

Conflicts of Interest:

None

Confidentiality:

All records will be kept confidential. Paper records will be kept in locked file cabinets in the office of the study coordinator. No names will be published in any publications resulting from this research.

Subject Compensation:

No financial compensation will be provided.

Facilities and Equipment

Device Sales Information

This study is an investigator initiated/sponsor initiated research study, utilizing devices which are commercially available for an unapproved indication. Those participating in the research study will not be charged for the device while participating in the study, and research participants will not be paid to participate in the study. The approval and conduction of the research study does not involve the sale or commercialization of the therapeutic use of the devices.

Device Labeling

Per the right of reference letter, all labeling information will be provided by Medtronic Neuromodulation, Inc.

Device Location

The stimulators are implantable devices and remain with participants involved. The study is based at George Washington University.

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