

ACUTE MODULATION OF STEREOTYPED HIGH  
FREQUENCY OSCILLATIONS WITH A  
CLOSED-LOOP BRAIN INTERCHANGE SYSTEM IN  
DRUG RESISTANT EPILEPSY

NCT05439655

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## IRB Minimal Risk Protocol Template

**Note: If this study establishes a human specimen repository (biobank) for research purposes, do not use this template. Use the Mayo Clinic Human Specimen Repository Protocol Template found on the IRB home page under Forms and Procedures at <http://intranet.mayo.edu/charlie/irb/>**

**First-time Use:** Use this template to describe your study for a new IRB submission.

1. Complete the questions that apply to your study.
2. Save an electronic copy of this protocol for future revisions.
3. When completing your IRBe application, you will be asked to upload this document to the protocol section.

**Modification:** To modify this document after your study has been approved:

1. Open your study in IRBe. Click on the study 'Documents' tab and select the most recent version of the protocol. Save it to your files.
2. Open the saved document and activate "Track Changes".
3. Revise the protocol template to reflect the modification points, save the template to your files
4. Create an IRBe Modification for the study and upload the revised protocol template.

## General Study Information

Principal Investigator: Nuri Ince Ph.D.

Study Title: ACUTE MODULATION OF STEREOTYPED HIGH FREQUENCY OSCILLATIONS WITH A CLOSED-LOOP BRAIN INTERCHANGE SYSTEM IN DRUG RESISTANT EPILEPSY

Protocol version number and date: Version 1. August 29, 2023

## Research Question and Aims

**Hypothesis:** We hypothesize that pathologic stereotyped HFOs can be captured with the implantable system such as the Brain Interchange (BIC) system of CorTec and spatial topography of these events can be utilized by t to deliver targeted electrical stimulation to achieve seizure control.

**Aims, purpose, or objectives:** The purpose of the research project to do data collection of EEG to determine whether new types of analysis of intracranial EEG including machine learning and sparse signal processing can add different and possibly useful information to standard types of analysis of intracranial EEG. Intracranial EEG data will be collected intraoperatively and postoperatively during routine clinical monitoring and will be analyzed by researchers for functional brain mapping and the investigation of high frequency oscillations (HFO's), for the purpose of identifying functional and epileptogenic brain areas. Patients will already have consented for an EEG as part of their standard of care procedure. This study will only involve collecting and analyzing EEG data for research purposes. The effects of cortical stimulation on high frequency oscillations will also be examined.



Mathematical modeling of the electrical activity from both intracranial and scalp EEG will be done to predict seizure onset region. Additionally, in the epilepsy monitoring unit (EMU), the acute electrical stimulation will be delivered to the HFO generating regions of the brain to investigate the modulatory effects of the targeted stimulation in suppressing the epileptic activity.

**Background** (*Include relevant experience, gaps in current knowledge, preliminary data, etc.*): Epilepsy is one of the most common neurological diseases. The overall incidence of the disease reaches a percentage between 0.5% ~ 2%. Nearly 30% of epilepsy subjects remain refractory to drug treatment, making surgical resection of epileptogenic zone an optimal solution to produce seizure freedom.

The success of epilepsy surgery requires accurate localization of epileptogenic zone, and minimal permanent injury to the surrounding normal brain tissue. High frequency oscillations (HFO) between 80 to 600 Hz, which can be recorded in human intracranial EEG (iEEG) data, are highly valued as a promising clinical biomarker for epilepsy and have been broadly studied since its discovery. Functional brain mapping using intracranial EEG data may be useful for both preoperative planning and intraoperative neurosurgical decision-making since it provides information on the anatomic localization of critical brain structures.

Because of the limited geographical extent that intracranial electrodes can feasibly cover areas of cortex, electrical source analysis of surface area and intracranial electrodes is often used to refine areas of investigation. In cases where surgical resection is not possible, responsive neurostimulation (cortical stimulation in response to detect seizures) for seizure abortion is a viable alternative.

## Study Design and Methods

### Methods:

Participation in this study is voluntary. The participating physician will identify any patients undergoing an intracranial EEG as part of clinical care.

For those subjects who agree to participate in this study, their intracranial EEG data will be collected in the operating room during the epilepsy surgery, and after the surgery in the epilepsy monitoring unit (EMU), in the same fashion as it would be without the study. We will record multichannel iEEG using an FDA approved bioamplifier and a benchtop research system (Brain Interchange System of CorTec) simultaneously. We will establish the efficacy of BIC in detecting HFOs and compare it to the FDA approved amplifier. During the recordings, this new device is NOT going to be implanted to the patients, but its benchtop version will be used simply to record neural data acutely without posing any additional risks. The neural signals obtained from already implanted electrodes will be streamed towards the BIC and FDA approved amplifier. Therefore, our work does not require any additional electrode implantations either.

The stored intracranial EEG data will be moved as computer files to the computers in the researchers' laboratory after deidentification. With offline analysis we will investigate the feasibility of capturing stereotyped HFO events using the benchtop BIC system and compare the detection results to those obtained with the commercially available amplifier. The data will be coded, and only completely coded data that contains no identifiers/deidentified will be analyzed in the neural engineering laboratory of Dr. Ince at Mayo Clinic.



These deidentified neural datasets will be processed using computational intelligence algorithms to predict the seizure onset zone and seizure freedom.

In particular, machine learning techniques and sparse signal processing methods will be employed to extract time-frequency features from the candidate HFO events captured following an amplitude threshold-based detector. An unsupervised algorithm will identify clusters of HFOs with similar waveform characteristics. Later the spatial distribution of these clusters and their temporal interactions will be computed and correlated with the functional brain mapping analysis and seizure onset zone. The results of computerized EEG analysis will be compared with imaging and other clinical information collected before and after intracranial EEG recording. This analysis will happen after the intracranial EEG data has been recorded for the purpose of planning epilepsy surgery, and this additional research analysis will not change the way that the subjects' EEG is recorded or the way that the EEG is used to plan the epilepsy surgery. Subjects will not need to do anything personally for the collection of the EEG data, and participating in the study will not change the EEG monitoring or treatment. Medical records at Mayo Clinic will only be accessed to obtain the EEG data for coding purposes and stripping data of identifiers. No other personal health information data is required for this study.

In addition, direct cortical stimulation will be accomplished in the operating room and EMU using established clinical parameters for functional mapping and the effects on high frequency oscillations will be examined during concurrent EEG recording. Cortical stimulation will be done for clinical purposes. Data will be obtained from the cortical stimulation as done within clinical practice.

During the last 1-2 days of the EMU monitoring, cortical stimulation will be delivered using established clinical parameters and iEEG will be recorded simultaneously. Scalp and intracranial EEG data will be collected as part of the standard clinical care. Both sets of EEG data will be analyzed quantitatively to predict probable seizure onset regions and modulatory effects of stimulation towards suppression of epileptic activity. We also plan to retrospectively review EEG data (without stimulation) of patients who have already had their evaluation.

### Subject Information

*Target accrual is the proposed total number of subjects to be included in this study at Mayo Clinic. A "Subject" may include medical records, images, or specimens generated at Mayo Clinic and/or received from external sources.*

Target accrual: 1000

Subject population (children, adults, groups): Adolescent (13-17 yrs), Adult (18-64 yrs), Child (3-12 yrs)

**Inclusion Criteria:**

Any patient with a diagnosis of refractory epilepsy, who is under the care of one of the investigators, and who will undergo intracranial EEG monitoring for clinical indications, who consent to be in the study.

**Exclusion Criteria:**

Any patient not undergoing EEG monitoring as part of their clinical course, or who do not consent to participate in the study. Neonates and children under the age of 3 will not be enrolled.

|                     |
|---------------------|
| <b>Biospecimens</b> |
|---------------------|

No Biospecimens will be collected.

|                                                     |
|-----------------------------------------------------|
| <b>Review of medical records, images, specimens</b> |
|-----------------------------------------------------|

Check all that apply (data includes medical records, images, specimens).

☐ Only data that exists before the IRB submission date will be collected.

**Date Range for Specimens and/or Review of Medical Records:**

Examples: 01/01/1999 through 12/31/2015, or all records through mm/dd/yyyy.

Note: The Date Range must include the period for collection of baseline data, as well as follow-up data, if applicable.

☒ The study involves data that exist at the time of IRB submission **and** data that will be generated after IRB submission. Include this activity in the Methods section.

Examples

- The study also plan to retrospectively review EEG data (without stimulation) of patients who have already had their evaluation
- The study plans to include subjects previously diagnosed with a specific disease and add newly diagnosed subjects in the future.

☐ The study will use data that have been collected under another IRB protocol. Include in the Methods section and enter the IRB number from which the research material will be obtained. *When appropriate, note when subjects have provided consent for future use of their data and/or specimens as described in this protocol.*

Enter one IRB number per line, add more lines as needed

☐ Data   ☐ Specimens   ☐ Data & Specimens \_\_\_\_\_

☐ Data   ☐ Specimens   ☐ Data & Specimens \_\_\_\_\_

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## Data Analysis

### Power Statement:

Data Analysis Plan: High frequency oscillations of iEEG are transients with 50-100ms duration. For these reasons, investigation of these events through visual inspection is difficult. For these reasons, computational methods involving unsupervised machine learning and neural signal processing will be employed to characterize high frequency oscillations in space and frequency. The computer will analyze massive prolonged iEEG recordings channel by channel and detect the HFO events in an automated fashion. Once the clusters of HFOs are identified, we will review the fast frequencies of iEEG activities and do brain functional mapping analysis. The results of computerized iEEG analysis will be compared with imaging and clinical factors to determine if there are correlations. The effects of cortical stimulation on the fast iEEG frequencies will also be examined. Computer analysis of the HFO activity will be correlated with the seizure onset zone and surgical outcome. Additionally, we will quantify the change in the rate of high frequency oscillations during and after the acute stimulation.

Scalp and intracranial EEG will be analyzed quantitatively to predict probable seizure onset regions. We will document our results by visualizing the distribution of HFOs in the brain. We will also document the rate and frequency characteristic of HFOs during different states such as sleep, awake, pre-ictal, post-ictal and cortical stimulation

### Endpoints

Primary:

Secondary: