Electrophysiologic Studies of Cognition in Epilepsy Patients
Correct NCT05769634 (incorrect on next page)
Principal Investigator: Allison Waters
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CONFIDENTIALITY STATEMENT

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Effective Date: 5/13/2025
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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the following:

United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

INVESTIGATOR'S SIGNATURE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines, as described in the *Statement of Compliance* above.

Principal Investigator or Clinical Site Investigator:

Signed:  Date: 2/22/2022

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1 PROTOCOL SUMMARY

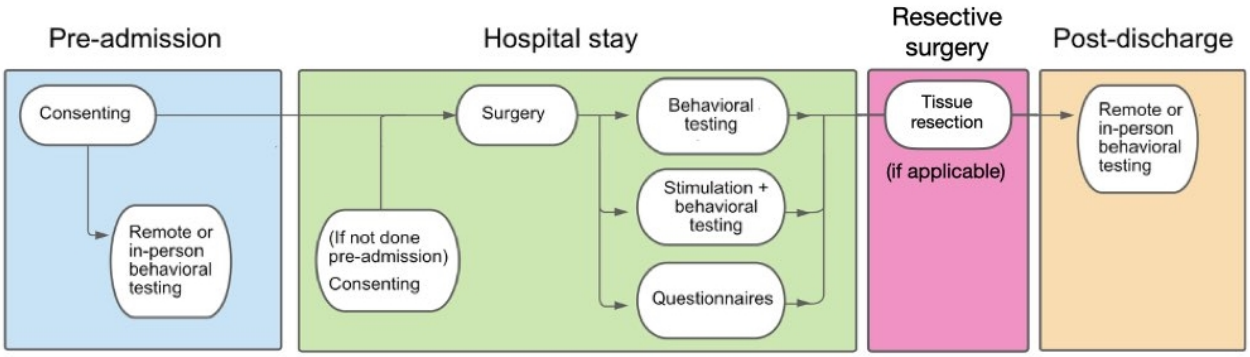
1.1 SYNOPSIS

Title:	Electrophysiologic studies of cognition in epilepsy patients
Study Description:	In this study, we seek to study how brain activity contributes to the generation of actions, emotions, memories, and other thought processes. To do that, we propose to examine brain activity recorded in patients undergoing neurosurgical interventions for treating epilepsy. Specifically, we leverage the fact that intractable epilepsy patients are surgically implanted with electrodes that allow recording the brain's electrical activity. Each electrode provides a readout of electrical activity in a different brain area, and therefore a way to measure brain activity in a very precise way, both anatomically and temporally, something that is very difficult to achieve otherwise in human subjects. We combine these recordings of electrical activity with tasks designed to test different aspects of behavior and thought, such as memory, decision-making, spatial navigation, etc. These take the form of short computer games that the patients will play while their brain activity is recorded using the clinically implanted electrodes. We will subsequently analyze the brain data, together with the patients' behavior and information about the location of each electrode, to derive information on how brain activity in different brain areas is related to behavior. In some cases, we will use special electrodes that allow very precise examination of neural activity (i.e. examine activation of single neurons, compared to large populations of neurons using other approaches) or use small amounts of electrical currents to stimulate specific brain areas to test their contribution to behavior. This will provide us with a more detailed understanding of the neurobiology of thought and provide causal observations of the contributions of individual brain areas. In a subset of patients that are clinically determined to undergo treatment resection, we will collect tissue samples for molecular analyses. This combination of electrophysiological recordings and behavioral tasks provide a unique opportunity to understand the contribution of brain processes to normal thoughts and behavior, as well as how these are affected in disease states (i.e. epilepsy, depression).
Objectives*:	Primary Objective: Study the neurophysiological basis of human cognition and actions.

Endpoints*:	The primary endpoint of this research is to investigate electrophysiological correlates of human cognitive and perceptual processes. The approach involves the analysis of the brain's electrical activity during computer-controlled cognitive/perceptual tasks, to determine how behaviors that occur during these tasks correlate with changes in electrical activity measured inside the human brain and on the scalp. The secondary endpoint of this research is to examine changes in neural activity and behavior in response to neurostimulation. The tertiary endpoint of this research is to characterize the genetic and molecular composition of human brain tissue to reveal important information about genetic differences in epileptic tissue and correlate electrophysiological and molecular biological measures to brain function and clinical diagnoses. The knowledge gained from these experiments will further our understanding of the brain's electrical activity and its relation to human cognition and disease. This increased knowledge base may lead to insights regarding better treatments for cognitive deficits and to improve epilepsy surgery and other therapies for seizure and other disorders. Further, uncovering the electrophysiological signatures of cognitive function through functional mapping, which enables the surgeon to avoid the resection of brain regions that could be especially crucial to cognitive function, may be improved, reducing the risk of post-surgical cognitive impairment following resection.
Study Population:	Epilepsy patients undergoing invasive monitoring.
Description of Sites/Facilities Enrolling Participants:	Mount Sinai Health System Hospitals and Epilepsy outpatient clinics.
Study Duration*:	An initial period of 10 years, to be extended as data collection continues.
Participant Duration:	Length of duration of intracranial EEG recordings in the Epilepsy Monitoring Unit (EMU; typical EMU stays range between 5-14 days) plus up to 12 months post-discharge.

1.2 SCHEMA

Study Design:



Research will be conducted at Mount Sinai West and Mount Sinai Hospital. Patients will be identified and recruited in either of these settings. Electrophysiological recordings will take place during patient stay in the Epilepsy

Monitoring Unit (EMU) of either site. Select tasks may need to be collected before hospital admission or after discharge; these will be carried out either in person during a patient visit to the hospital or remotely through a computer screen in the patients' preferred setting (i.e. at their homes) through a computer browser.

Mount Sinai may act as the coordinating institution across several research institutions involved in research. In such case, all sites will carry out research following all NIH and IRB guidelines and regulations. We will establish a research reliance and/or data transfer agreements with Mount Sinai as necessary.

1.3 SCHEDULE OF ACTIVITIES

Patients will participate in the study for the duration of their hospitalization (typically 5-14 days in the EMU; 1 day for participation in placement of the microelectrodes during surgery). In some cases, patients will be asked to complete one or several remote behavioral tests (computer games) before they are admitted or after they are discharged from the hospital. In the case of pre-operative testing, the available time window will occur between consenting and EMU stay, typically a few weeks. Consent will take place preoperatively or on surgery day. If patients undergo resective surgery and consent to research use of resected tissue, this portion will happen at the time of resection, determined on clinical grounds. For post-operative testing, patients will be asked to carry out behavioral testing one or several times over the 12 months following EMU discharge.

	Pre-operative	Surgery Day	Epilepsy monitoring unit stay (typically 5-14 days)	Resective surgery (if applicable)	Post-discharge (up to 12 months)
Informed Consent	X	X			
Demographics			X		
Clinical history	X	X	X		X
Obtain tissue				X	
Outcome Evaluation					
Quality of Life Questionnaire			X		X
Task Administration	X		X		X
Adverse Events Reporting			X		X

2 INTRODUCTION

2.1 STUDY RATIONALE

The study aims at understanding the neural substrates of language, attention, motor control, emotion and memory processing; as well as developing techniques to improve neurosurgical treatment of seizures and brain abnormalities. These approaches will assess the functional connectivity and communication between cortical regions involved in human cognitive processing. It will provide neuroanatomical, electrophysiological neurostimulation and behavioral information about the neural circuits involved in decision-making, attention, motor control, emotion and memory. This will ultimately help us improve clinical treatment of neurosurgical patients.

2.2 BACKGROUND

Although one can crudely measure the human brain's electrical signals by recording from the scalp, the ability to observe and measure oscillations generated in local regions of the brain requires recordings taken from electrodes implanted in the brain (i.e., invasive EEG, or iEEG recording). Such iEEG recordings are often clinically required in the surgical treatment of severe medication-resistant epilepsy (i.e., seizure disorders that are not controlled by standard drug therapies). For these patients, surgery is potentially curative; the goal in planning surgery is to precisely localize the brain areas responsible for seizure activity. This can be accomplished by monitoring iEEG recordings over a period of several days to several weeks.

Intracranial EEG monitoring furthermore enables the study of single-neuron activity using hybrid "micro-macro" electrodes that contain additional microwire bundles exiting from the tip of the standard clinical electrodes. This minor modification provides a rare and important opportunity to study the human nervous system as a single-cell resolution in awake, behaving humans. This paradigm has led to key insights into epileptic seizure generation and propagation, as well as human cognition.

In addition, electrical brain stimulation is a routine procedure in the EMU for localization of brain function and is frequently performed in patients with intracranial electrodes. By studying how electrical stimulation elicits changes in oscillatory activity related to epilepsy or cognition, we may be able to causally discern the specific brain circuits involved. Electrical stimulation also provides the opportunity to measure changes in neurotransmitter concentration via voltammetry techniques that have been utilized in rodents for 25 years, and human subjects more recently, and can assess how critical neurotransmitters such as dopamine, serotonin, and norepinephrine fluctuate in relation to human cognitive performance.

iEEG recordings therefore offer a rare and valuable opportunity to record neurophysiological activity directly from the human brain, compare these results with those from animal models and to extend these insights into unniquelyl human cognitive capabilities (for example in decision-making or abstract reasoning). iEEG recordings have already been used to greatly enhance our knowledge of the physiology of human cognition by allowing investigating local cortical dynamics in an awake human, how different cortical areas interact to generate cognition and actions, to assess the formation and propagation of seizures, and to carry out causal interrogations of brain activity (Saez 2018, Sani 2018, Helfrich 2018, Kahana 1999, Fried 2014, Parvizi 2013, Desmurget 2009).

In addition, resective surgeries, which are a possible treatment outcome post-iEEG evaluation, offer a possibility to recover human tissue for subsequent molecular analysis and characterization. This offers unique possibilities to characterize the genetic and molecular composition of human brain tissue, which could reveal important

information about genetic differences in epileptic tissue, and allow correlating electrophysiological and molecular biological measures.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

EMU patients will be under standard neurology and nursing care with video/medical monitoring in the EMU. Note that these patients typically have their medications tapered during their stay in order for them to have seizures, which is the goal of the clinical monitoring. In the event of a seizure, standard protocols will be followed on the unit. Again, patients are supposed to have multiple seizures during this stay in the EMU. A member of the study team will always be present during the testing required for this study, including testing that involves stimulation.

- Cognitive testing: all cognitive and memory tests are designed to be minimally difficult. Some subjects may find the tests to be stressful, tiring, or boring. Cognitive testing will not interfere with their epilepsy monitoring or treatment. Standard medical care and safety protocols during EMU admission will not be altered by participation in this study. If an intervention is medically required due to the occurrence of seizures or post-ictal complications (including but not limited to the administration of sedating or anticonvulsant medications, resuscitative measures including supplemental oxygen, or patient restraint for safety in the setting of post-ictal agitation), the cognitive testing will be aborted and/or deferred until a time when the patient's medical condition permits continuation of the testing. Procedures to mitigate risks of cognitive testing: session times will be minimized, and assessments may take place over more than once session, if needed and appropriate. Participants may also take breaks, as needed. Subjects have the right to refuse to answer questions they feel are too distressing, as well as to terminate any one part or the whole of their participation at any time.
- Single neuron recordings: we will use augmented macro-micro electrodes that include, in addition to the macro contact sites routinely used for clinical recordings, micro contact filaments to allow electrophysiological recordings that can isolate individual neurons. There is no additional risk of intracerebral hemorrhage or tissue injury compared with the standard clinical macro electrodes. There are no reports of any ill effects from these FDA-approved electrodes for clinical EEG recording. Recordings from the microelectrode filaments that protrude from the macro electrode shaft do not interfere with the usual clinical recordings and have the potential to significantly improve some aspects of mapping seizures and cognition. Every study examining the design and safety of such micro-macro depth electrodes has found them to be as safe and effective as standard depth electrodes for intracranial monitoring (House 2006, Van Gompel 2008, Waziri 2009, Hefft 2013, Misra 2014, Carlson 2018). Their use requires no extra surgical procedures. Procedures to mitigate risks of single neuron recording: we will only use single-unit recording electrodes in locations targeted for clinical reasons. The locations and number of sEEG electrodes will therefore be based on clinical necessity and will not be changed due to participation in this study. Only a subset of sEEG electrodes (typically 1-4) will be replaced by macro-micro electrodes.
- Brain stimulation: we do not anticipate any significant increase in risk, since we will be using FDA-approved electrodes and stimulating according to clinical protocols. Stimulation will be carried out using macro electrodes only, even if the patient consented to microelectrode implantation. It is possible that brain stimulation could produce a seizure that causes injury. We will monitor the occurrence of seizures producing injury in all enrolled patients. Patient safety will be tracked by the PI and research staff in real time and reported to the Mount Sinai IRB according to the guidelines in HRP-214. Procedures to mitigate stimulation testing risks: to minimize the risk of triggering a seizure through stimulation, we will limit stimulation to levels routinely used by the clinical team for functional mapping (≤6mA). Stimulation testing will only be carried out once the patient has been cleared

for explantation by the clinical team, to minimize risks of elicited seizures prolonging the patients' medical stay. Stimulation will only occur using macroelectrodes.

- Privacy: the risk of loss of private information, however small, is always present when PHI is shared by a patient, as well as when data is shared among study personnel and collaborators. However, we will take every precaution to prevent this. Each participating patient will be assigned a unique identification number and there will be no reference personal identifiers in any subsequent publication. All personal identifiers will be destroyed upon completion of the research and the required storage period. Data files will be stored on a secured server, which will be password-protected and access to data files will be given only to IRB approved research personnel. The main risks of audio and video recordings performed in this protocol are associated with patient privacy. Patients will be fully informed that their face and voice will be identifiable to the team members analyzing the data. While recordings will only be associated with a participant's study ID, it is not possible to fully de-identify facial images. Procedures to mitigate privacy risks: The risk of disclosure of PHI will be adequately conveyed to participants in the informed consent document for this study. The study investigators and research staff will abide by all policies and procedures set forth by Mount Sinai and in accordance with Good Clinical Practices with respect to the proper storage and transfer of PHI and other subject data. Only the minimal amount of patient information, including that which is personally identifiable, will be accessed in the conduction of this study.
- Tissue resection: tissue resection will be carried out adhering to clinical protocols, with all research activities being carried out on the resected tissue. Therefore, no additional risks are estimated.
- Unforeseeable risks: this study may involve risks that are currently unknown and unforeseeable. Procedures to Mitigate Unforeseeable Risks: All new information, including new risks and that which may affect a person's decision to continue study participation, will be disclosed as it becomes available.

2.3.2 KNOWN POTENTIAL BENEFITS

We anticipate no direct benefit to enrolled patients. This fact will be communicated to the patients. However, this research may benefit future patients through a better understanding of the activity of brain regions involved in cognition and disease.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Through the risk mitigation strategies outlined above, risk to the patients is kept to a minimum, whereas there is large potential for improving our understanding of brain function and disease.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
Primary			
Investigate the neurophysiological correlates of human cognitive processes. The approach involves the analysis of the brain's electrical activity during computer-controlled cognitive/perceptual tasks, to determine how behaviors that occur during these tasks correlate with changes in electrical activity measured inside the human brain and on the scalp.	*The primary endpoint for each task tested will be the number of estimated subjects required for appropriate powerful statistical testing –an estimated 10-20 subjects depending on the*	*Achieving appropriate statistical power for each task.*	*Measuring neuronal activity in neuronal populations.*

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
	anatomical coverage of individual patients.		
Secondary			
Investigate the causal involvement of individual brain areas in cognitive processes through targeted electrical stimulation.	*The primary endpoint for each task tested will be the number of estimated subjects required for appropriate powerful statistical testing –an estimated 10-20 subjects depending on the anatomical coverage of individual patients.*	*Achieving appropriate statistical power for each task.*	*Modulation of neuronal activity and behavior through neural stimulation.*
Tertiary			
Characterize the genetic and molecular composition of human brain tissue to reveal differences in genetic expression and its relationship to electrophysiological and clinical measures.	*The primary endpoint will be the number of estimated subjects required for appropriately powerful statistical testing for each clinical diagnosis, comorbidity or electrophysiological metric under study–an estimated 20 subjects per set.*	*Achieving appropriate statistical power for transcriptomics studies.*	*Gene transcription patterns in resected tissue.*

4 STUDY DESIGN

4.1 OVERALL DESIGN

Overview: this is a prospective observational study. We will recruit adult patients who are undergoing intracranial electroencephalographic (iEEG) or regular EEG monitoring as part of a standard clinical procedure for the treatment of pharmacologically resistant epilepsy. iEEG monitoring is used by physicians to pinpoint seizure foci and to map areas of the brain that give rise to seizures. In addition, this method is used for brain stimulation mapping in order to characterize areas that are critical for cognitive function. Patients will be from the clinical population at MSSM undergoing monitoring. Potential study subjects are discussed at epilepsy Surgical Conferences and the clinical team will identify and flag candidates that meet the inclusion criteria. Subjects will be approached prior to surgery or upon arrival in the epilepsy monitoring unit the day after the electrode implantation surgery, and will be informed that they will receive the same standard of care whether or not they choose to participate in the research. Informed consent will be obtained from all participants. No patient will be excluded on the basis of race, gender or ethnicity. The main goal of the current project is to study the neurophysiological basis of human cognition across brain areas, which will be accomplished through behavioral testing, electrophysiological recordings and brain stimulation.

Behavioral testing: The main objective of this project is to record neurophysiological activity during cognitive and behavioral tasks during the patients' EMU stay. Patients will primarily complete behavioral tasks for the duration of their EMU stay, for as long as they're willing to participate. We will present them with cognitive tasks while we record

iEEG, so that we can help define critical brain areas for decision-making, memory, and other cognitive processes. The same electrodes used clinically will be used for the cognitive tasks. We will present these patients with images or video clips on a computer monitor, sounds through headphones, or taps to different fingers. They will be asked to pay attention to and remember the different pictures, sounds or taps. They also may be asked to press a button in response to certain stimuli or make movements with their hands, make a verbal response, or make a series of choices involving uncertain outcomes (e.g., money). In some cases, audio recording may be conducted as part of the experimental procedure, with the patient speaking into a microphone and the speech recorded. The patient may be asked to say out loud individual phonemes, words, or complete sentences out loud. If a verbal response is recorded, the recordings will be assigned a subject identifier number that is also assigned to other data from the experiment. Conducting and administering cognitive and memory tests poses no clinical or safety risks to the patient. All tests will be scheduled around patient clinical needs and will interfere in no way with patient clinical schedule and events. Typically, recording sessions will take about 60-90 minutes, for a total of 2-5 hours total. The patient can stop the recording session at any time and for any reason.

Remote testing: In some instances, patients will be asked to complete behavioral tests (i.e. computer games) prior to or after their hospital stay, as specified above (Section 1.2). These are necessary in some cases in which the scientific validity of the research requires preliminary training or testing, or subsequent re-testing or validation. Patients will complete remote testing accomplished in-person during hospital visits or through remote testing in internet-connected devices (e.g. laptop or tablet). The patient will be given the option to complete testing in either modality. If the patient prefers the remote option, s/he will be offered a research-owned device in which to carry out testing, or be instructed on how to access the task through a computer program (i.e. a browser). If the patient chooses the device, s/he will be allowed to keep it until their involvement with the research program is complete.

Electrophysiological recordings: Study subjects will be patients with intractable medication resistant epilepsy who are candidates for scalp EEG or iEEG monitoring, meaning they will have electrodes surgically inserted either subdurally (grids/strips) or into the brain (depth electrodes). These electrodes are part of their standard clinical treatment, and electrode locations will not be altered in any way for this research. During recordings, we may add a connector from our behavioral testing computer to the clinical recording computer (Saez 2018); this device will have no effect on patient clinical monitoring or outcome and it is solely intended to allow time synchronization of our testing computer with the recording computer, and it has been approved for use by clinical engineering. Neurologists and nurses will be available and on-call should any other clinical safety issues arise as part of the patient's stay in the hospital. Electrophysiological recordings will be carried out using the clinical recording system, and in some cases additionally using a research dedicated system.

Video recordings: Video recording during invasive epilepsy is part of standard of care treatment. We will record video of the patient during their hospital stay, and in some instances analyze it to contribute to research analyses, for example to verify patient's behavior during different times of the day or facial expression during tasks.

Modified electrodes: For single neuron recordings, we will use augmented macro-micro electrodes that include, in addition to the macro contact sites routinely used for clinical recordings, micro contact filaments to allow electrophysiological recordings that can isolate individual neurons. There is no additional risk of intracerebral hemorrhage or tissue injury compared with the standard clinical macro electrodes. There are no reports of any ill effects from these FDA-approved electrodes for clinical EEG recording. Recordings from the microelectrode filaments that protrude from the macro electrode shaft do not interfere with the usual clinical recordings and have the potential to significantly improve some aspects of mapping seizures and cognition. Every study examining the design and safety of such micro-macro depth electrodes has found them to be as safe and effective as standard depth electrodes for intracranial monitoring (House 2006, Van Gompel 2008, Waziri 2009, Hefft 2013, Misra 2014,

Carlson 2018). Their use requires no extra surgical procedures. The locations and number of sEEG electrodes will be based on clinical necessity and will not be changed due to participation in this study. Only a subset of sEEG electrodes (typically 1-4) will be replaced by macro-micro electrodes. Thus, these micro-macro electrodes provide unique and safe opportunities to study the human brain at single-neuron resolution during the performance of cognitive tasks. If the patient consents to the use of microelectrodes and chooses to withdraw from study at any time, the microelectrodes will be removed during the explantation procedure of the standard of care electrodes to minimize risk to the patient.

Brain Stimulation: Electrical brain stimulation is a routine procedure in the EMU for localization of brain function and is frequently performed in patients with intracranial electrodes. We plan to use similar focal currents, using macroelectrodes to stimulate the brain, during cognitive tasks to help localize and define cognitive networks. The patient's baseline performance on specific tasks will be established on trials without stimulation and compared to trials with stimulation in specific regions and statistically analyzed. For stimulation, we may employ the stimulation hardware routinely used for clinical mapping (e.g. Nicolet cortical stimulator) or an equivalent research device (e.g. ATLAS Stim Headbox - High Density, part number: 31-0601-0132) using identical stimulation parameters as specified below. The electrical current will be kept at or below the same safe levels as used in standard clinical cortical mapping. Safety limits have been established for decades (McCreery, et al. 1990; Gordon et al., 1990, Shannon 1992). Here, we will apply stimulation while subjects perform cognitive tasks at levels far below the safety limits identified by histological analysis for stimulation protocols (McCreery, et al. 1990; Gordon et al., 1990). Stimulation studies will be performed using currents not exceeding 10mA, below the accepted safety limits for charge density (Shannon 1992), and in line with previous studies. There is no evidence that stimulation of the type to be performed in this study causes any patient risk. The only significant change to the patient's routine in the proposed studies is that brain stimulation will be performed for longer periods and sometimes in different locations than required for standard evaluation. Patients will be asked frequently if they would like to continue or stop testing, and testing will be halted at any signs of patient discomfort or fatigue. Electrical stimulation also provides the opportunity to measure changes in neurotransmitter concentration via voltammetry techniques that have been recently developed for safe use in human subjects (Kishida 2018).

Resected tissue analysis: in some cases, the determined clinical strategy for intractable epilepsy patients involves removal of epileptiform clinically determined to be the focal origin of seizure activity. This is an effective treatment strategy, which is employed in a subset of patients that undergo iEEG monitoring, and which is determined strictly on clinical grounds. This provides a valuable research opportunity to characterize the resected tissue with molecular and genetic tools (e.g. *in situ* gene expression) in a way that, like the electrophysiological component of this study, is not otherwise possible.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

iEEG recordings taken during treatment for intractable epilepsy have already been used to greatly enhance our knowledge of the physiology of human cognition. First, iEEG recordings sample from smaller brain volumes than scalp-recorded EEG or magnetoencephalographic (MEG) signals, are not subject to distortions produced by the human skull, and are relatively impervious to movement artifacts because of their high signal- to-noise ratio. iEEG recordings also offer far better temporal resolution than functional magnetic resonance imaging (fMRI). In addition to providing an opportunity to investigate the local cortical dynamics in an awake human, iEEG allow us to study how different cortical areas interact to produce dedicated functions, to assess the formation and propagation of seizures, and to causal interrogations of brain activity. We will be using the same electrodes placed for clinical purposes, and will not remove, replace, or add additional electrodes unless it is clinically indicated or as

contemplated below. The resulting datasets will provide a depiction of brain activity with superb anatomical and temporal resolution and a high signal to noise ratio typically unavailable in studies of human brain function. Similarly, the tissue analysis portion of the study, which provides a unique possibility to study the genetic and molecular composition of human brain tissue, will be only carried out when there is a clinical determination to use resection as a treatment.

4.3 JUSTIFICATION FOR INTERVENTION

Leveraging existing clinical interventions will allow us to carry out detailed electrophysiological and molecular studies on human brain activity at a level of temporal and anatomical resolution otherwise unavailable to neuroscientific research.

4.4 END-OF-STUDY DEFINITION

Study completion can happen through one of the several mechanisms:

- Completion of study procedures
- Withdrawal of participant consent
- Withdrawal of participant by study investigator
- Clinical safety endpoints

Procedures for Subjects to Request Withdrawal: Procedures to withdraw from the protocol are conveyed to participants in the informed consent document, which requires the formal withdrawal of consent in writing to the Principal Investigator of the study. Subjects will be advised that information already collected in the study may not be removed from the research study database and will continue to be used to complete the research analysis. Patients may also withdraw permission for the use and disclosure of any of protected information for research purposes by notifying the Principal Investigator in writing. However, the Principal Investigator may still use the information that was already collected if that information is necessary to complete the research study and/or data analyses. As this is not a treatment study, study withdrawal will not impact subjects' ongoing clinical care.

Procedures for Investigator to Withdraw Subjects: Participants will be notified that the Principal Investigator has the right to withdraw any subject from the protocol at her discretion without patient consent, which is conveyed in the informed consent document. Potential reasons for participant withdrawal include: termination of the research, subject non- compliance with study protocol (particularly that which compromises patient safety or renders data collected to be unusable), or patient inability to complete study procedures as required (which renders data collected to be unusable).

Clinical safety endpoints: We will immediately terminate a patient's participation in the study if this is deemed necessary by the clinical team. In addition, the PI will monitor the study for any adverse events (AEs), although we do not anticipate any given the nature of the study. Adverse events, any untoward medical occurrence in a subject during participation in the study including include any sign, symptom, abnormal assessment (laboratory test value, vital signs, electrocardiogram finding, etc.) or combination thereof, will result in termination of the patients' participation in the study. The AE will be documented by the research team and reported to the IRB using IRB communication channels. If action is deemed appropriate to ensure patient safety by the IRB following AE review, the research team will implement these changes in all future participants.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

We will enroll patients who have pharmacologically resistant epilepsy who are undergoing invasive electroencephalogram (iEEG) monitoring as part of their standard care.

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Is able to provide written informed consent.
- Is a candidate to receive iEEG for Epilepsy.
- Is willing and able to comply with all study-related appointments and procedures.
- Has English language proficiency or an available translator for all study procedures.
- Is over the age of 10.

No patient will be excluded on the basis of race, gender, or ethnicity. Underage subjects (children 10 years and older) will be considered for inclusion after obtaining both patient and parental consent. Consent will be obtained when a minor enrolled in the study attains 18 years of age.

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

- Has cognitive or physical impairments that would limit their ability to participate in testing.
- Is unable to consent.
- Is pregnant (Note: Pregnant women are not candidates for intercranial EEG monitoring).
- Is a prisoner.
- Is under the age of 10.

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

This protocol will recruit patients who are undergoing intracranial electroencephalographic (iEEG) monitoring as part of a standard clinical procedure for the treatment of pharmacologically resistant epilepsy. Potential iEEG surgical candidates present to Mount Sinai epilepsy clinic at a rate of approximately 30-40 a year. Of these, based on past data we expect about 50-75% to be capable of participating in the tasks based on our inclusion criteria, for an expected data collection rate of about 20 EMU patients/year. We plan to collect 200 patients over the course of the first 10 years of study.

- How participants will be identified: Epilepsy patients are discussed at weekly epilepsy clinical meetings in which the clinical team will identify candidates that meet the inclusion criteria. Epilepsy monitoring unit (EMU) patients will be approached prior to surgery or upon arrival in the EMU and will be informed that they will receive the same standard of care whether they choose to participate in the research or not. Informed consent will be obtained from all participants. Future recruitment materials will be submitted for IRB review as a protocol modification, as needed.
- Consenting of underage participants: consent will be obtained from the patient and an accompanying parent or legal guardian. When the minor turns 18, they will be asked to consent again.
- Who will initially approach potential participants: Study Personnel, Treating Physician, Principal Investigator of referring protocol.

- Patient Incentives: Patients will be compensated for completing tasks. Most tasks will offer a flat compensation for completion (typically $10). When required by the research, an additional variable payment will be added. This is essential for the scientific validity of some tasks that are designed to test brain responses to reward (e.g. decision-making tasks), on which reward must be tied to performance. Despite this constrain, we will guarantee the fairness of the tasks by having a minimum $10 payment for completion regardless of performance. Payment will be provided as a gift card after the end of the study. We will only provide compensation for non-military personnel. If patient is underage (<18 yo), payment will be provided to parents or legal guardians.
- Costs: All costs associated with this study are paid for by research funds. The cost of macro-micro electrodes and study-specific cognitive testing will be provided by the study and not charged to the patient nor insurance. The patient's surgery and other standard medical care including their stay in the EMU will be billed to the patient and or insurance.

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

6.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

N/A.

6.2 LOST TO FOLLOW UP

This study does not involve any follow-up after completion.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

N/A.

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

N/A.

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

N/A.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request without penalty. Their withdrawal from the study will not affect their clinical care. If subjects withdraw from the research for whatever reason, the recorded data will be kept, unless specifically asked by the subject to be withdrawn. Patients can withdraw from the study at any time and for any reason.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

The following non-safety assessments with take place as part of this study:

Screening and evaluation: After providing study-specific informed consent, potential participants will be formally evaluated for eligibility and study inclusion. Participants will provide demographics and contact information. Per the informed consent document, additional information will be collected from the electronic medical record, including diagnoses, current medications, medical / treatment history, neuroimaging studies (pre/postoperative MRI, CT), and others as applicable.

Assessment battery: participants may complete self-report cognitive and psychological assessments at each study visit (including for example scales of depression, apathy, anxiety, and obsessiveness/compulsivity such as the Beck Depression Inventory and Beck Anxiety Inventory). Each of these assessments takes approximately 5 minutes to complete, and this part of the study is anticipated no last more than 30 minutes. Additional disorder-specific assessments may be used at research visits to quantify clinical symptoms unique to each patient's neuropsychological assessment.

If the suicide item of the DI questionnaire (question #9) is rated 2 or greater (regardless of total score), the study member will notify the PI, who will contact the referring physician within 24 hours. If any subject is in acute distress at the time of intake, their doctor will be contacted immediately, for care as needed.

Additional measures of psychopathology, affect, anhedonia, motivation, personality, and motor function may be performed when requested by a referring study PI or clinician. Assessments will be performed by a licensed clinical psychologist, physician, or trained member of the research staff in accordance with administration standards for each measure. These may be obtained from the electronic medical record if performed as part of routine care, if available.

Access to medical records: As part of recruitment and research efforts, the research team will review mental health and psychotherapy records prior to consent. This is necessary to identify patients who should be excluded from the study as per our inclusion/exclusion criteria, and also because this information will be important for the scientific validity of our findings. For example, co-morbid pathologies such as anxiety or depression, which are common in intractable epilepsy patients, can strongly affect behavior in some of the cognitive tasks and behaviors under examination, and knowing whether a previous diagnosis exists and its severity is essential for interpretation of the data.

8.2 SAFETY ASSESSMENTS

We will continue to track patient safety data as usual for all patients in the epilepsy monitoring unit. We maintain an electronic database in which we record complications. We will report any new information or safety events per Mount Sinai IRB.

To protect participants against fatigue, frequent breaks will be offered during every session. Research sessions will be immediately interrupted for any health-care-related needs. Involved physician and nursing personnel, as well as the research team will carefully attend to the comfort of every participant. Participants will be made aware of their right to discontinue a session at any time, without repercussion.

Provisions for Research Related Harm or Injury: The subject should promptly tell the person in charge of the research if they believe that they have been injured because of taking part in this study. If a subject is injured as a result of study participation, Mount Sinai will provide necessary medical treatment. Depending on the circumstances, the costs of the treatment may be covered by Mount Sinai Health System or may be billed to the insurance company just like other medical costs. Mount Sinai does not normally provide any other form of compensation for injury.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS

An adverse event (AE) is any untoward medical occurrence in a subject during participation in the clinical study or with use of the experimental agent being studied. An adverse finding can include a sign, symptom, abnormal assessment (laboratory test value, vital signs, electrocardiogram finding, etc.), or any combination of these.

A serious adverse event (SAE) is any adverse event that results in one or more of the following outcomes:

- Death
- A life-threatening event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- An important medical event based upon appropriate medical judgment

CLASSIFICATION OF AE SEVERITY

AEs will be labeled according to severity, which is based on their impact on the patient, using a 1-4 scale. An AE will be termed “mild” (1) if it does not have a major impact on the patient, “moderate” (2) if it causes the patient some minor inconvenience, “severe” (3) if it causes a substantial disruption to the patient’s well-being and “life-threatening” (4) if it causes complications that can result in death.

8.3.1.1 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

AEs will be categorized according to the likelihood that they are related to the study intervention using a 0-5 scale. Specifically, they will be labeled definitely unrelated (0), unlikely (1), potentially related (2), probably related (3) or definitely related (4) to the study intervention.

- Definitely Unrelated (0) – The AE is completely independent of study procedures administration, and/or evidence exists that the event is definitely related to another etiology.
- Unlikely to be related (1) – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study procedures administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study procedures) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant’s clinical condition, other concomitant treatments).

- Potentially Related (2) – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of study procedures). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- Probably Related (3) – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study procedures, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal.
- Definitely Related (4) – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study procedures administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study procedures should be clinically plausible. The event must be pharmacologically or phenomenologically definitive.

8.3.2 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs, not otherwise precluded per the protocol, will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study procedures (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical or psychiatric condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. Documentation of onset and duration of each episode will be maintained for AEs characterized as intermittent.

The PI's team will record events with start dates occurring any time after informed consent is obtained until the last day of participation in the hospital stay portion of the study. Events will be followed for outcome information until resolution or stabilization.

8.3.3 ADVERSE EVENT REPORTING

The PI will monitor the study for any AEs, although we do not anticipate any given the nature of the study. Adverse events will be documented by the research team and reported to the IRB using IRB communication channels. If action is deemed appropriate to ensure patient safety by the IRB following AE review, the research team will implement these changes in all future participants. In addition, if necessary (i.e. multiple AEs are reported) the PI and the research team will maintain a log of all AEs.

SAEs that are unanticipated, serious, and possibly related to the study intervention will be reported to the Independent Monitor and IRB in accordance with requirements.

- Unexpected fatal or life-threatening AEs related to the intervention will be reported within 7 days. Other serious and unexpected AEs related to the intervention will be reported within 15 days.
- Unrelated SAEs will be handled in a less urgent manner but will be reported to the Independent Monitor, IRB and other oversight organizations in accordance with their requirements.

8.3.4 SERIOUS ADVERSE EVENT REPORTING

In consultation with the PI, a trained member of the study team will be responsible for conducting an evaluation of a serious adverse event and shall report the results of such evaluation to the NIH and the reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 10 working days after the investigator first learns of the event.

DESIGNATION OF AN INDEPENDENT MONITOR

The Independent Monitor for this study is Dr. Sophia Ryan (Dept. of Neurology, Icahn School of Medicine). Dr. Ryan is not associated with this research project and thus works independently of the study team. Dr. Ryan is not a part of the key personnel involved in this project, and is qualified to review the patient safety data generated by this study because of her expertise in Neurology.

8.3.5 REPORTING EVENTS TO PARTICIPANTS

N/A.

8.3.6 EVENTS OF SPECIAL INTEREST

N/A.

8.3.7 REPORTING OF PREGNANCY

N/A - pregnant women are excluded from the study.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Primary endpoints: Investigate the neurophysiological correlates of human cognitive processes. We hypothesize that modulations in neural activity, as recorded by electrophysiological or electrochemical techniques, will be associated with different cognitive aspects of the behavioral tasks that the patients will complete. Specifically, we expect that cognitive brain functions will localize to a variety of brain areas, including temporal and prefrontal regions, with electrophysiologic signatures in the theta (4-8Hz) and high-gamma (70-200 Hz) frequency ranges. Scientists have theorized that cyclic changes in the brain's electrical activity (brain oscillations) play a fundamental role in memory function. Studies have focused on the theta (slow) rhythm which oscillates in the 4-8Hz frequency range and high gamma activity which appears in the 70 to 200 Hz frequency range because these neural signatures appear prominently during a wide range of cognitive tasks and are hypothesized to be the cause of all neural activity - our thoughts, feelings and perceptions. The relationship between brain oscillations and neuronal activity is largely unexplained so our study aims to investigate the correlation between brain oscillations and the neuronal activity of

human cognition. We will also investigate the contribution and information processing capabilities of individual neurons.

Secondary endpoints: investigate the causal involvement of individual brain areas in cognitive processes through targeted electrical stimulation. We hypothesize that modulation of brain electrical activity through targeted stimulation will reversibly affect patient behavior. Specifically, we expect that stimulation of prefrontal cortical areas (i.e. orbitofrontal cortex) will result in changes in associated behavior (for example, in choices during decision-making behavior) that will be sampled through behavioral tasks.

Tertiary endpoints: characterize the genetic and molecular composition of human brain tissue to reveal important information about genetic differences in epileptic tissue and correlate electrophysiological and molecular biological measures to brain function and clinical diagnoses. We hypothesize that there will be significant association between expression of individual genes (e.g. related to synaptic function such as neurotransmitter receptors, voltage-gated ion channels, GPCRs) and (1) clinical diagnosis (e.g. epilepsy type, psychiatric comorbidities) and (2) neurophysiological activity (e.g. theta [4-8Hz] or high-gamma [70-200 Hz] frequency power, oscillatory coherence, etc.) as recorded in the deep temporal lobe area prior to resection.

9.2 SAMPLE SIZE DETERMINATION

The primary analyses will compare the difference in neural activity at individual electrodes depending on behavioral or computational regressors or classifications. Based on previous studies, we expect sample sizes of 10-20 patients to be sufficient to examine activation in individual brain regions of interest. With an estimated average of 2-4 iEEG electrodes per region per patient, this will result in sample sizes of 20-80 electrodes. Given that prior studies show only a subset of electrodes is active in response to specific conditions of regressors, with activation rates ranging between 5-30%, a difference of 10 $\mu V^2/Hz$ in power activation in a specific frequency band (e.g. high gamma), this sample size will have >90% power to detect this difference using a two-sided test at $\alpha=0.05$.

Conversely, the main outcome measure for stimulation experiments will often be behavioral parameters, i.e. risk attitudes during decision-making tasks. Assuming a difference of 10 points in risk preferences (in line with prior results) scores, this sample size will have > 85% power to detect this difference using a two-sided test at $\alpha=0.05$.

9.3 POPULATIONS FOR ANALYSES

There is no patient segmentation, and all patients that complete a specific behavioral task will be included in analyses.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

To identify association between behavioral and neural metrics, we will use a regression approach where the dependent variable was defined as the analytic amplitude of the neural time series. For trial-based analyses, the neural time series is subsequently divided into event-related epochs, normally averaging neural activity using a rolling window at (e.g. 200ms width, with 50ms increments). To identity task-selective channels, we performed separate linear regressions of average neural activity on each behavioral regressor of interest. Given the inter-trial variability in response latencies, this analysis may be performed separately time-locked to each behavioral event of

interest (i.e. task presentation, patient response). We use the resulting R^2 (variance in the neural data that can be explained by the behavioral regressors of interest, % explained variance, %EV) as a metric of the quality of the fit. This approach is insensitive with respect to time of task-related activation and to the direction of encoding (i.e., increases or decreases in neural activity). Electrodes will be classified as task active for any given regressor if they show a significant correlation ($p < 0.05$) at 5 or more consecutive time windows at any point during the epochs. False positive rate will be determined using a permutation strategy. For each regression, we will shuffle the relationship between behavioral labels and neural activity 1,000 times, and take the resulting distribution as the null for that particular regressor-electrode combination. In the case of single neuron analyses or voltammetry recordings, we will use the spiking activity or recorded neurotransmitter concentration as the variable of interest in a similar fashion.

In the case of multiple regressors of interest, we will verify that the encoding profile of individual electrodes is not affected by regressor collinearity, for example by using a stepwise regression model. In summary, the analysis for each electrode proceeded as follows: first, we will carry out multiple individual linear regressions for all regressors. To leverage the time profile of the signals without imposing restrictions on activation timing, an aggregate statistic was calculated as the sum of F-stats for the longest stretch of consecutive significant (linear regression $p < 0.05$) windows. We will repeat this procedure 10,000 times after shuffling the behavioral labels, and take the proportion of permuted fits with a sum-of-F-stat higher than that in the original dataset was taken as the permutation p value. This p value will be further corrected for multiple comparisons using a Bonferroni correction (across n electrodes); regressors that did not survive multiple comparisons will be considered not active. Subsequently, we will seek to identify the set of regressors that best explain neural activity variance by performing a model selection procedure on the surviving regressor set. We will first select the regressor that explains the most variance in the neural data (maximum peak %EV) as the base model, then create an alternative complex model by incorporating the second regressor that most improved the model. These two models will be compared using an ANOVA test; if the complex model results in a significantly improved fit (ANOVA $p < 0.05$), we will reject the basic model. This process will be iteratively repeated by adding new regressors, sorted by residual %EV improvement, until the model cannot be further improved (ANOVA $p > 0.05$). Finally, we will estimate the proportion of electrodes encoding each variable across all electrodes, regardless of the order in which they were incorporated into the model. To verify that the results were not driven by inter-subject or inter-electrode variability, we may conduct mixed-effects model analysis using the concatenated HFA for all electrodes as dependent variable, round-by-round regressors of interest (risk, regret, etc.) as fixed effects, and patient and electrode ID as nested mixed-effects.

In the case of behavioral analyses (i.e. for secondary endpoints), behavioral metrics or latent model parameters will be estimated from the behavioral data. To compensate for potential variability across patient behavioral strategies and behavior, we will whenever possible employ a within-subject analysis by completing a baseline behavioral task pre-stimulation (either before or during hospital admission). If possible, we will also test for lingering behavioral effects by carrying out behavioral testing post-stimulation.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

The main goal of the study is to understand the neurophysiological basis of human cognition. This will require integrated analysis of clinical, neurophysiological, anatomical, video and behavioral datasets.

Analysis of Electrophysiological Data: Some of the analysis will be performed at Mount Sinai, and some will be performed at collaborating sites. Any data sent to other sites will be de-identified. Typically, iEEG recordings are amplified x10000, analog filtered (0.01-1000 Hz) with > 1kHz digitization rate, re-referenced to a common average or bipolar reference scheme offline and high-pass filtered at 0.1-1 Hz with a symmetrical (phase true) finite impulse response (FIR) filter (35 dB/octave roll-off). Channels with a low signal-to-noise ratio (SNR) are identified and deleted

(i.e., 60 Hz line interference, electromagnetic equipment noise, amplifier saturation, poor contact with cortical surface). Additionally, channels are visually inspected by a neurologist or research team member to exclude epochs of aberrant or noisy activity (typically < 1% of data points). A photodiode recorded screen updates in the behavioral task, recorded in the electrophysiological system as an analog input and used to synchronize behavioral and electrophysiological data. In some cases, different synchronization (through an audio feed into an analog channel or through TTL pulses) may be carried out. Data analysis is carried out in MATLAB and R using custom scripts and electrophysiological analysis toolboxes (e.g. Fieldtrip). Data for each channel is down sampled to 1KHz and filtered into high-frequency activity (HFA; 70–200 Hz) using a two-way, zero phase-lag, finite impulse response band pass filter to prevent phase distortion. Alternatively, time-frequency representations are created using wavelets, or equivalent methods, using linearly or logarithmically spaced frequencies, which allows for comparisons between time-varying high-frequency and low-frequency signals on an equal footing. This is especially important for iEEG signals, which are generally nonstationary and have time-varying phase components. We will also measure coherence and phase synchronization to quantify the degree to which oscillatory effects are synchronized across brain regions.

When analyzing physiological data recorded at many electrode sites for effects at many frequencies, it is necessary to correct for multiple comparisons. Using standard statistical methods, such as a t-test or a Wilcoxon rank-sum test, and setting an arbitrary p-value threshold for the significance of the difference between two conditions does not account for the possibly high number of false positives by chance. Therefore, to generate an unbiased empirical estimate of the Type I error rate, we will use a bootstrap procedure, a method often used to handle correlations among statistical comparisons of electrophysiological measures. The bootstrap procedure first entails generating a large number (>1000) of random samples of the experimental data by randomly swapping items from each of the categories being compared. The same randomization is used across electrodes to control for between-electrode correlations. By running the statistical tests on each of the shuffled datasets one generates a distribution of statistics from which one can then determine the statistical threshold that would achieve a given Type I error rate.

Analysis of video data: A video recording of the patients will be obtained, either through the standard video-EEG procedure included as part of the standard of clinical care or through a dedicated research video camera in the same room. The video data may be analyzed to identify patient behavioral or mood states (e.g. sleep, awake, communication, laughing, etc.). These analyses will be carried out either by research personnel or using dedicated software. The resulting datasets will be kept in a secure location together with the electrophysiological and other data from the patient.

Electrode Localization: For the proposed research, electrode locations are determined using co-registered postoperative CTs and preoperative MRIs by an indirect stereotaxic technique (Talairach & Tournoux, 1988). After normalization, locations can be reported by means of stereotaxic (Talairach) coordinates. This format uses three numbers (X, Y, Z) to describe the distance from the Anterior Commissure (the “origin” of Talairach space). The X, Y, Z dimensions refer to left- right, posterior-anterior, and ventral-dorsal, respectively (i.e., 38 X 64 X 58 mm refers to a point in the right-posterior-dorsal region of the brain). Region-of-interest analyses can be conducted and better compared across participants by normalizing the brain using Talairach coordinates. The Talairach atlas serves as a reference so that one may know what region of the “idealized” brain is being described. These techniques are commonly used at Mount Sinai now and may aid in clinical patient care by providing accurate anatomical localization for individual electrodes.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

The secondary endpoints will involve analysis of behavioral modulation resulting from electrical modulation of neuronal activity. As such, they will be task specific, but in most instances this will entail estimation of a behavioral (for example, proportion of remembered items in a memory task) or computational (derived from behavior through the application of computational models) metric of interest in pre-stimulation (baseline) and stimulation conditions. We will carry out within-patient comparisons to account for inter-patient variability, and in most instances will carry out two-tailed statistical tests (e.g. two-tailed t-test) to compare individual behavioral/computational estimates.

9.4.4 ANALYSIS OF THE TERTIARY ENDPOINT(S)

The tertiary endpoints will involve analysis of genetic expression data and comparison across comorbidities or electrophysiological features of interest. For example, we will plan to examine differences in genetic expression profiles across depression comorbidity status (e.g. depressed/non-depressed) and severity (e.g. Beck Depression Inventory score). We will perform multivariate analyses between transcriptomic expression data and clinical scores or electrophysiological features (e.g. individual frequency band oscillatory power) as appropriate and use permutation/bootstrapping methods to assess statistical significance.

9.4.5 SAFETY ANALYSES

N/A.

9.4.6 BASELINE DESCRIPTIVE STATISTICS

For all analyses, we will keep track of the patients' demographic information (age, sex, handedness, neuropsychiatric test results) and include these as covariates in analyses as necessary.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

EMU subjects will be approached prior to surgery or upon arrival in the epilepsy monitoring unit and will be informed that they will receive the same standard of care whether or not they choose to participate in the research. Patients who consent upon arrival to the EMU will not be eligible to participate in the microelectrode portion of the study because their electrodes would have been already placed at that point but could participate in the other portions of the study. Informed consent will be obtained from all participants. The subjects will be asked to consent to the following (note: patients can consent to one or more of these portions, without consenting to all of them):

- Collection of electroencephalographic (EEG) and invasive EEG (iEEG), Radiology Studies and Clinical history.
- Cognitive testing.
- Use of Microelectrodes in addition to standard electrodes.
- Brain stimulation mapping in addition to what is required clinically.
- Use of resected tissue.

Non-English speaking patients will only be allowed to participate in the presence of a translator.

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Research staff will communicate with treating clinicians/ISMMS researchers to inform them about the protocol, who will identify potential participants and ascertain his/her interest in the study. Individuals who are potentially eligible (see Inclusion-Exclusion criteria) and agree to consider participating in the study will be consented by a member of the research team. All personnel involved in recruitment will have undergone all appropriate HIPAA and CITI training, as per institutional policy.

Participant Screening: If an individual is interested in pursuing study participation, he/she would be invited to meet with the research team, provide written informed consent, and be formally evaluated for study inclusion. Study inclusion/exclusion criteria will be reviewed with participants. Patients will provide demographics and contact information, a list of current medications, and information regarding his/her epilepsy status. In addition, this information may be retrieved from the participant's medical record, as well as previous neuroimaging studies (pre/postoperative MRI, CT) and neuropsychological assessment. Subjects will only be consented by study staff who are not providing clinical care, to avoid undue pressure to participate. All personnel involved in evaluation and enrollment will have undergone all appropriate HIPAA and CITI training.

This study will only enroll patients who have the capacity to provide informed consent. Capacity to consent will be made by the individual conducting the informed consent discussion with the participant. If a subject cannot comply with the consent process or there is a question on the part of the assessor as to the fitness of the individual to participate in the research as prescribed, the subject will be excluded from study participation and not be permitted to sign the informed consent document. In the case of underage (<18) iEEG patients, assent will be obtained from the participant and consent from at least one parent.

This protocol will not exclude participants based upon race nor sex/gender. Patients will have to exhibit English language proficiency; otherwise, a qualified translator (i.e. a bilingual member of the research team, or a qualified translator) must be present for consent and all study procedures. In this case, study assessments will be presented in the relevant language.

Consent forms describing in detail the study intervention, study procedures, and risks will be given to the participant and written documentation of informed consent will be completed prior to starting the study intervention. The following consent materials are submitted with this protocol:

- Consent form for adult patients (>18 years of age).
- Consent form for underage patients' parents or legal guardians. (<18 years of age).

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the funding agency. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor/funding agency and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule. Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants

- Insufficient compliance of study staff to the protocol (i.e., significant protocol violations)
- Data that are not sufficiently complete and/or evaluable

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the funding agency, sponsor, IRB, Food and Drug Administration (FDA), or other relevant regulatory or oversight bodies (OHRP, DSMB).

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, the safety and oversight monitor(s), and the sponsor(s) and funding agency. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally-identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor or funding agency, representatives of the Institutional Review Board (IRB), regulatory agencies or representatives from companies or organizations supplying the product, may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor/funding agency requirements.

Some study participant research data, which is for purposes of statistical analysis and scientific reporting, may be transmitted to and stored at NIH repositories. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by NIH research staff will be secured and password protected.

Measures Taken to Ensure Confidentiality of Data Shared per the NIH Data Sharing Policies: it is NIH policy that the results and accomplishments of the activities that it funds should be made available to the public (see *https://grants.nih.gov/policy/sharing.htm*). The PI will ensure all mechanisms used to share data will include proper plans and safeguards for the protection of privacy, confidentiality, and security for data dissemination and reuse (e.g., all data will be thoroughly de-identified and will not be traceable to a specific study participant). Plans for archiving and long-term preservation of the data will be implemented, as appropriate.

Certificate of Confidentiality: to further protect the privacy of study participants, the Secretary, Health and Human Services (HHS), has issued a Certificate of Confidentiality (CoC) to all researchers engaged in biomedical, behavioral, clinical or other human subjects research funded wholly or in part by the federal government. Recipients of NIH funding for human subjects research are required to protect identifiable research information from forced disclosure per the terms of the NIH Policy (see *https://humansubjects.nih.gov/coc/index*). As set forth in 45 CFR Part 75.303(a) and NIHGPS Chapter 8.3, recipients conducting NIH-supported research covered by this Policy are required to establish and maintain effective internal controls (e.g., policies and procedures) that provide reasonable assurance that the award is managed in compliance with Federal statutes, regulations, and the terms and conditions

of award. It is the NIH policy that investigators and others who have access to research records will not disclose identifying information except when the participant consents or in certain instances when federal, state, or local law or regulation requires disclosure. NIH expects investigators to inform research participants of the protections and the limits to protections provided by a Certificate issued by this Policy.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for specific tasks in this study will be analyzed and stored at the NIMH Data Archive (NDA). After the study is completed, the de-identified, archived data will be transmitted to and stored at the NDA, for use by other researchers including those outside of the study. Permission to transmit data to research repositories will be included in the informed consent.

If tissue resection analyses are carried out, the resected biological tissue will be stored until the molecular and genetic characterization is carried out (typically 2-3 weeks).

10.1.5 KEY ROLES AND STUDY GOVERNANCE

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Additional Research Personnel: Research staff affiliated with this protocol have combined expertise in neuroimaging analysis, biomedical engineering (signal processing, hardware development, software programming), iEEG and single neuron data collection and analysis, diagnostic and clinical assessments of neurological and psychiatric populations, and clinical trial development and administration. In addition, the current research team has developed methods to acquire, manage, and analyze data collected specifically from individuals with implanted invasive electrodes.

Assurance of Staff Familiarity with the Protocol: While conducting research under this protocol, all members of the research team participating in this study must have complete and up-to-date Collaborative IRB Training Initiative (CITI) and HIPPA training, and all must be familiar with relevant study procedures and documents commensurate with his/her role on the project. Further, weekly C-ACT laboratory and clinical meetings will include thorough discussion of pertinent study-related issues, and the multidisciplinary, team-based approach to research and clinical matters which is the foundation of the Center will ensure continuity of care and additional monitoring of subjects for potential adverse events.

10.1.6 SAFETY OVERSIGHT

Study will be monitored internally by clinician members of the study team. As an added precaution, we will have an independent Medical Research Monitor available for consultation and safety oversight. As Medical Research Monitor, Dr. Sophia Ryan will be available for consultation to provide expert medical recommendations in case of any serious adverse events. Dr. Ryan is a trained Neurologist, Chief of Inpatient General Neurology and Medical Director of Quality and Safety at Mount Sinai West Hospital. Dr. Ryan is independent of the research team and she will promptly report any adverse events to the IRB. Additionally, Dr. Ryan will also review the case details of any adverse event and determine whether any modifications to the protocol are needed in order to further minimize risks.

10.1.7 CLINICAL MONITORING

Study will be monitored internally by clinician members of the study team.

10.1.8 DATA HANDLING AND RECORD KEEPING

We will maintain appropriate medical and research records for this trial, in compliance with ICH GCP and regulatory and institutional requirements for the protection of confidentiality of participants. As part of participating in a NIH-sponsored or NIH-affiliated study, we will permit authorized representatives of the NIH, sponsor, and regulatory agencies to examine (and when permitted by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity.

10.1.8.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

De-identified intracranial and/or scalp EEG data, radiology studies, pathology reports, cognitive testing results, video recordings, Epilepsy Surgical Conference notes, Operative notes and Tissue samples (if resections are carried out) will be obtained. All data will be stripped of identifying information and stored with an identifier as a reference. Names and participant numbers will only appear together on a single list stored in a password-protected file, and will only be accessible to the research team. Access to all files is and will continue to be restricted to the Principal Investigator and the research team.

How Media Will Be Stored to Ensure Confidentiality: the data will be stored securely on encrypted servers behind the Mount Sinai firewall, which comply with all applicable Mount Sinai policies and procedures including HIPPA and IT data integrity and security. Data and PHI accessed from local workstations are within the Mount Sinai network and are housed behind the institutional firewall. Remote access from offsite will employ VPN. All other personal identifying information (e.g. participant name, medical record number, etc.) will be removed from audiovisual data. Video recordings will only be identified by study-specific subject ID. However, as videos will include full face images of research participants, it is not possible to fully de-identify this media. This risk to participant privacy is clearly conveyed to potential research subjects in the informed consent document.

How PHI will be protected from improper use or disclosure: all PHI, including subject audiovisual recordings, will be stored in secured locations. Electronic PHI will be kept stored on a physically secured server in a password protected database which adheres to all Mount Sinai data security standards. Access to PHI will be limited to research staff and collaborators who require this information to conduct study-related tasks and data analyses. Data will be coded and identified only by study-specific ID. Information containing PHI, including audiovisual recordings, will be stored separately from other deidentified research data. The code which links study ID with patient identity via direct identifiers will be stored separately from other study data in a physically and/or electronically secure location, with access limited to certain research staff requiring this information to ensure quality of clinical care, regulatory compliance, and research operations.

Steps that will be taken to secure the data during storage, use, and transmission: whenever possible, PHI will be separated from other data, and deidentified data will be accessed by study personnel or transmitted to study collaborators who do not require personal identifiers to perform protocol-related activities. Data transmitted outside of the Mount Sinai network will be encrypted. When not in use, data, including PHI, will be kept in locked files in the C-ACT offices. Data will be accessed from password protected workstations and servers, which have been configured to limit physical and electronic access by unauthorized persons.

10.1.8.2 STUDY RECORDS RETENTION

PHI (research/HIPAA records) will be stored for 6 years after the close of the study (per the Mount Sinai Investigator Manual). De-identified data will be stored indefinitely. If patients elect to withdraw from the study, they will be advised that information already collected in the study may not be removed from the research study database and will continue to be used to complete the research analysis. Patients may also withdraw permission for the use and disclosure of any protected information for research purposes by notifying the Principal Investigator in writing. However, the Principal Investigator may still use the information that was already collected if that information is necessary to complete the research study and/or data analyses. This is conveyed to potential participants in the study informed consent document.

Tissue samples will be kept until the molecular analysis are carried out, typically a few days and no more than a month. The techniques we are proposing are destructive, so the tissue will be destroyed during experimentation.

10.1.9 PROTOCOL DEVIATIONS

The PI will monitor the study for any adverse events (AEs), although we do not anticipate any given the nature of the study. Adverse events will be documented by the research team and reported to the IRB using IRB communication channels. If action is deemed appropriate to ensure patient safety by the IRB following AE review, the research team will implement these changes in all future participants.

In addition, if necessary (i.e. multiple AEs are reported) the PI and the research team will maintain a log of all AEs using the format specified in Appendix (AE log table).

SAEs that are unanticipated, serious, and possibly related to the study intervention will be reported to the Independent Monitor and IRB in accordance with requirements:

- Unexpected fatal or life-threatening AEs related to the intervention will be reported within 7 days. Other serious and unexpected AEs related to the intervention will be reported within 15 days.
- Unrelated SAEs will be handled in a less urgent manner but will be reported to the Independent Monitor, IRB and other oversight organizations in accordance with their requirements.

10.1.10 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication. This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, data from tasks classified as clinical trials will be registered at ClinicalTrials.gov, and results from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 5 years after the completion of the primary endpoint by contacting PI Saez. Considerations for ensuring confidentiality of these shared data are described in Section 10.1.3.

10.1.11 CONFLICT OF INTEREST POLICY

Dr. Fedor Panov (a co-investigator in this study) receives financial compensation as a lecturer for Zimmer, the company that manufactures the device used to implant the intracranial electroencephalogram (EEG). Dr. Panov also receives financial compensation as a lecturer for Neuropace, a company that manufactures implantable devices used in the treatment of epilepsy.

10.2 PROTOCOL AMENDMENT HISTORY

*The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A **Summary of Changes** table for the current amendment is located in the **Protocol Title Page**.*

Version	Date	Description of Change	Brief Rationale
2	3 April 2025	The protocol has been modified to include collection of resected tissue samples from patients who undergo resective surgery. Additionally, approved stimulation hardware has been expanded to include an equivalent research device (e.g. ATLAS Stim Headbox - High Density, part number: 31-0601-0132).	Collection and molecular analysis of resected tissue would offer unique possibilities to characterize the genetic and molecular composition of human brain tissue, which could reveal important information about genetic differences in epileptic tissue, and allow correlating electrophysiological and molecular biological measures. Inclusion of additional stimulation hardware would streamline the stimulation research protocol.

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