Official Title:	High-density EEG in Neurological Disorders
NCT number:	NCT04266041
Document Type:	Study Protocol
Date of the Document:	03Jan2024

MINIMAL RISK CLINICAL RESEARCH PLAN

CPHS template v. 4/17/2017

Please complete: D-HH# 30813 PI: Yinchen Song, Krzysztof A. Bujarski

Important Note: The CPHS Department (Chair & Scientific) Review Form is required with this application. Find the form in the RAPPORT Library or on the CPHS Website.

- **DO NOT USE this form for retrospective chart review studies. Please use the Data Specimens Registries Research Plan.**
- **Respond to each item, even if to indicate N/A or not applicable**
- **Attach and/or upload this form as your 'Investigator Protocol' in Rapport**
- **If you are completing this form on a Mac, indicate your answer to any checkboxes by bolding or highlighting, or by deleting any incorrect options.**

1. Introduction and Background

This study will focus on obtaining a special type of scalp EEG recordings (high-density EEG) and electrical impedance measurements in patients with neurological disorders (i.e., epilepsy, brain tumor, stroke, etc.) and appropriately matched controls. High-density EEG (hdEEG) is a scalp EEG which uses up to 256 channels compared to the standard 21 channels used for routine clinical applications. The reason for using more channels to record is for more precise localization of epileptogenic foci and/or more precise mapping of brain functions. To that end, it is optimal to utilize subject's own MRI scan to create the modeling for hdEEG analysis. Electrical impedance can be measured using the same electrodes as EEG or other electrodes interspersed between the EEG electrodes or placed at other anatomic locations. Electrical impedance provides a measure of electrical tissue properties as opposed to brain function by injecting safe and imperceptible current (I) at a given frequency into selected pairs of electrodes and recording the corresponding voltage differences (V) across other electrode pairs, i.e. $Z = V/I$. By using high-density electrodes, much like hdEEG, electrical impedance measurements can be combined to produce an image of the electrical properties of the brain tissue (a process called Electrical Impedance Tomography (EIT)). Alternatively, a smaller subset of electrodes can be used to acquire measurements over a frequency range (a process called Electrical Impedance Spectroscopy (EIS)) that can yield gross information across regions of the tissue. All of these techniques (EIT, EIS and hdEEG) may provide clinically useful information for a number of neurological disorders where there is significant change to brain tissue.

2. Objectives and Hypotheses

This study is aimed at 1) using scalp high-density EEG (hdEEG) for localizing epileptic activity and/or studying brain functions in patients with certain neurological disorders, and 2) using the same (or similar interspersed) electrodes to acquire electrical impedance images (EIT) or record spectral impedance signatures (EIS) of neurological disorders. The experiments that we perform will involve measurement of brain activity and tissue in patients with neurological disorders (i.e., epilepsy, brain tumor, stroke, etc.) and controls using a novel scalp hdEEG system and custom EIT/EIS systems.

hdEEG: We plan to localize the sources of interictal epileptiform activity during resting state for patients with seizures, and map brain activity during presentation of tasks. The development, testing and refinement

of the various tasks will be an ongoing process of multidisciplinary collaboration among a variety of co-investigators representing the Department of Psychiatry (P. Holtzheimer), Department of Neurology (Y. Song, K. Bujarski, E. Kobylarz, B. Jobst, D. Rojas-Soto, T. Lukovits), and Section of Neurosurgery (L. Evans, J. Hong, and J. Aronson). Testing will investigate the localization of a wide variety of brain functions, including: sensation, movement, hearing, vision, speech, memory, social cognition, and emotion. As such, a variety of hypotheses regarding the localization of specialized brain functions and their disruption by certain neurological disorder processes will be evaluated in the course of this work. The purpose of this study is to use the hdEEG for improved localization of critical brain functions important for further understanding of the brain in health and disease, and also planning surgical intervention if warranted.

EIT/EIS: EIT and EIS represent promising technologies to image or characterize the brains of stroke patients because there are significant conductivity differences between normal, ischemic, and hemorrhagic (blood) tissue. This electrical information may help to 1) identify the onset of a stroke, 2) discriminate hemorrhagic from ischemic stroke, 3) provide reliable automatic and continuous monitoring of stroke patients after stabilization aims will be an ongoing process of multidisciplinary collaboration among co-investigators representing the Department of Neurology (Y. Song, K. Bujarski, E. Kobylarz, B. Jobst, D. Rojas-Soto, T. Lukovits) and the Thayer School of Engineering (E. Murphy, R. Halter, A. Everitt).

3. Study Design

Describe all study procedures, materials, and methods of data collection:

hdEEG System: High-density EEG recordings will be obtained via the EGI Geodesic EEG 400 designed for research applications. This system is available through the Department of Neurology and Department of Psychiatry at DHMC. This EEG system uses a 256 (or 128) channel cap to record EEG signals during the resting state and during the performance of functional or cognitive tasks.

EIT/EIS Systems: The EIT and EIS data collection will use custom systems owned by the Thayer School of Engineering at Dartmouth and housed in the Williamson Building at DHMC. The EIT/EIS data collection will be conducted only on stroke patients and healthy control subjects in this study. Electrical impedance systems are well established as patient safe and are commonly used in bioelectrical body impedance analysis [a], lung monitoring [b], breast cancer research [c], stroke research [d] and other research. **EIT system**. The EIT system (Fig. 1A) is a broadband (100 Hz–10 MHz) 20-channel data acquisition (DAQ) system with a SNR > 90 dB which possesses high speed capabilities (up to 80 frames/ second) [e]. The system is flexible and has a modular hardware and software design that allows for performance upgrades such as DAQ frame rate and SNR. It uses National Instruments (NI) hardware and software modules, which offer inherent compatibility over generations of hardware and software revisions. Digital switches allow data to be recorded from up to 120 electrodes. **EIS system**. The EIS system operates similarly to the EIT system. However, it will only use up to 30 channels. The custom-designed system allows for switching between channels and applies currents over a bandwidth of 100 Hz-500 kHz. Prior versions of both the EIT and EIS systems have been safely implemented in other IRB-approved human subjects studies here at DHMC [f] The EIT and EIS systems comply with International Electrotechnical Commission (IEC) requirements for safety and essential performance of medical electrical equipment (IEC 60601-1). The EIT system has been reviewed and approved by DHMC Biomedical Engineering. The EIS system is the next iteration of this and will be approved by DHMC Biomedical Engineering prior to any patient use.

Optical Scanners:
The optical scanners are used to recover precise locations of electrodes and landmarks, e.g. nasion (bridge of nose), left and right pre-auricular points, for registration with the MR imaging data. The scanners will either be a Geodesics Photogrammetry System 3 (GPS3) (https://www.philips.com.tw/healthcare/product/HC4601902/geodesic-photogrammetry-system-3-research-

gps) or a research-only iPhone/iPad (password protected) using a 3D scanning application. The GPS3 software allows via a semi-automated process to output electrode and landmark positions. Thus subjects' photographs will be immediately deleted after positions are output. The iPhone/iPad application (i.e., Heges, Capture) performs all 3D scanning calculations locally and scans will immediately be transferred to approved research computers and original scans on the iPhone will be deleted. Secondary, checks will be performed on the scans and if any identifiable information remains in the scans they will be removed.

Studies

There will be three types of studies: short-term hdEEG study, short-term hdEEG/EIT/EIS study, and long-term hdEEG study. For short-term study, the study duration is up to 2 hours. For long-term study, it will be at least an overnight recording.

1) Short-term hdEEG study (Epilepsy, Brain tumor, Peripheral nerve)

A patient with neurological disorder (i.e., epilepsy, brain tumor, peripheral nerve dysfunction, etc.) or control subject will be studied as an outpatient in the EEG lab. The subject will have the 256 or 128-channel cap placed and a special type of photograph of the EEG cap and subject's head will be taken using a Photogrammetry system which allows for better source modeling of electrophysiological signals. The subject will subsequently recline on a chair or bed and either rest (i.e., attempt to fall asleep) and/or perform specific tasks. We expect that experiments will usually be completed in 1 session lasting 60-120 minutes. For patients with peripheral nerve dysfunction, we expect to conduct 2 sessions of recording, one before their surgical procedure, and one during their post-operative follow-up visit to assess the peripheral nerve function recovery.

2) Short-term hdEEG/EIS/EIT Study (Stroke, Control)

Patients recently stabilized after an acute stroke or healthy volunteers serving as control subjects will be recruited and consented to participate in this study. Control subjects and patients that can safely be transported will have data collected in the EEG lab, where all of the EEG equipment is normally located. Patients that cannot be transported will have their data collected in their inpatient room. A cap will be placed on their head with up to 256-channels for EEG and EIT and up to an additional 30 EIS electrodes (described below). A special type of photograph of the EEG cap, other electrodes and patient's head will be taken using either the Photogrammetry system in 3C or a portable optical scanning unit described previously. The 3D scan of the head, cap, and electrodes produced via photogrammetry allows for better modeling of electrical tissue parameters and sources of electrophysiological signals. Patients will subsequently recline on a chair or bed and either rest (i.e. try to fall asleep) or perform specific tasks. We expect the experiment will be completed in a session lasting approximately 90-120 minutes. We will record 1) 10 minutes of resting state hdEEG, 2a) ~10 minutes of EIT data from the EEG cap electrodes and/or 2b) ~30 minutes of EIS data from a subset of electrodes, and 3) an additional ~20 minutes of hdEEG while the study participant performs a sensorimotor assessment. NIH stroke scale/score (NIHSS) and general clinical information (i.e., type of stroke, laterality, etc.) will be assessed by consenting physicians. A second data collection may be performed at 2-3 months post-stroke during a routine outpatient follow-up appointment, based on the patient's condition and willingness to participate. At this visit, the same protocol will be performed, and NIHSS may be assessed.

A brain MRI scan may not be part of their standard care, we will obtain permission to access their head CT scans, if available. Otherwise, we will use a standard brain atlas (https://www.mcgill.ca/bic/software/tools-data-analysis/anatomical-mri/atlases/mni-305) for their hdEEG analysis.

On a subset of ~15 patients (based on budget constraints) a brain MRI scan may also be performed during follow-up appointments. If an individual is not able to participate in the MRI scan for any reason, they will not be excluded from the study. Subject can choose not to participate in the follow-up MRI scan. MRI scan that is done solely for study purposes will not be billed to subject's insurance. Incidental findings, if any, will be shared with the subject (and their LAR, if applicable) and documented in their medical records.

Pregnant persons will be excluded in this study. Persons of childbearing age will be questioned regarding pregnancy in addition to undergoing a urine pregnancy test before MRI scan. If the urine pregnancy test is

positive, the subject will be excluded. Subjects will be told the results. Because full confidentiality regarding pregnancy cannot be entirely guaranteed, these testing requirements and the limited scope of confidentiality will be made known to the subject during the consent procedure. In this manner, anyone who would not be comfortable with pregnancy testing or sharing the results of such testing can "opt out" of the study at the time of the initial consent, without having to declare any specific reasons.

For control subjects, we will not obtain their individual MRI scans. Instead, we will use the standard brain atlas (https://www.mcgill.ca/bic/software/tools-data-analysis/anatomical-mri/atlases/mni-305) for the hdEEG analysis.

3) Long-term hdEEG study (Epilepsy)

Patients with epilepsy admitted to the Epilepsy Monitoring Unit (EMU) will be consented to participate in this study on one of the days of his/her admission. A 128-channel (or 256-channel) long-term monitoring (LTM) net (gel-based) will be placed on the patient's head in the EMU. hdEEG will be recorded overnight in addition to the clinical video-EEG. There will be no control subject enrolled in this study. We expect the experiment will be completed in 6-24 hours, depending on the subject's specific situation. A special type of photograph of the EEG cap, other electrodes and patient's head will be taken using either the Photogrammetry system in 3C or a portable optical scanning unit described previously.

hdEEG Data Management

The primary form of data analysis will be the extraction and localization of event- or task-related EEG signals using synchronous averaging and other more sophisticated forms of signal extraction.

For some experiments, normal controls will be enrolled and their test and task scores will be used for comparison purposes. EEG data will be collected from these participants.

We will be presenting participants with a variety of tasks designed to activate regions important for language, motor, sensory, auditory, visuospatial, emotion, social cognition or memory function. The tasks used will depend on the specific situation of the patient, region of seizure onset or lesion, or type of surgical procedure planned. For instance, if patient has left frontal lobe epilepsy, language tasks may be given for characterization and localization of language areas.

In order to map the motor and sensory areas, we will ask the patient to tap their fingers on the thigh periodically during the movement task. By doing so, the mu-rhythm (8-12 Hz) will predominantly appear around the primary motor and sensory cortices. However, such activity can be easily affected by artifact and is not specific to any type of movement (i.e., arms or legs). Peripheral nerve somatosensory evoked potential (SSEP) tests will also be conducted in order to reliably activate the somatosensory area during the sensory task. A clinical evoked potential recording system (i.e., Medtronic NIM E4) will be used to send a constant current stimulus through surface electrodes to subjects' peripheral nerves (i.e., ulnar, median, tibial, etc.). The stimulation parameters used to trigger the somatosensory evoked potential will follow the ACNS guideline (https://www.acns.org/pdf/guidelines/Guideline-9A.pdf). The SSEP raw data will be recorded using the hdEEG system. Other potential tasks to be used in this study will be to ask patients to speak, read, name pictures, remember words, remember actions and shapes, and to view shapes or objects. At certain instances, patients may be asked to view emotionally charged pictures or videos. Using these images is important to study and localize social and emotional brain function. For instance, the type of pictures presented may include selected pictures taken from IAPS (International Affective Picture System, https://pdfs.semanticscholar.org/09bb/229a610acdd3150b8e0176194e7b7cf471b7.pdf). In all tasks, only pictures and/or videos specifically vetted by the IRB will be presented.

De-identified EEG data and images collected for this study will be shared with other institutions and added to public databases of EEG data. All data released will be de-identified.

The data being released is EEG data (basically digitally encoded brain waves). The data variables include:
Spike – single epileptic spike (for epilepsy patients)
Event Marker – start and end of each event

EIT/EIS Electrodes

The EIT data collection will be accomplished only by means of the hdEEG scalp cap electrodes. The EIS data collection may use a small subset of hdEEG electrodes and additionally 1) electrodes placed at the base of the skull (standard ECG, stick-on electrodes), 2) custom orbit electrodes (applied to the skin surface) (see Fig. 1C), and 3) soft-palate electrodes (see Fig. 1B). The orbit electrodes will make contact with the skin on opposite sides of the nose without contacting the eye. The soft-palate electrodes are standard surface EMG electrodes which are secured to a sterile lattice which sits safely on the roof of the mouth (much as a mouth guard would). Alternatively, standard flexible Ag/AgCl hydrogel (Cadwell) electrodes which do not require the rigid lattice to secure to the roof of the mouth may be chosen to improve patient comfort. Data from the soft-palate electrodes will only be collected in 3 minute windows at the beginning and end of the session, at which time the patient will be closely monitored to eliminate the possibility of choking. Furthermore, both the orbit and all soft-palate electrodes are single-use and will be replaced between patients, and all scalp electrodes will be sterilized between uses.

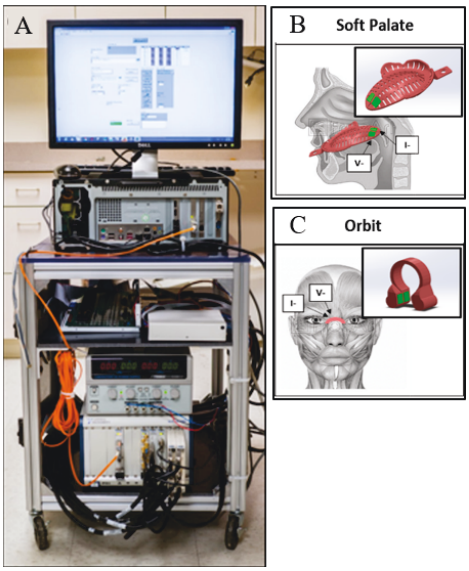

Figure 1. A. Custom 20-channel EIT system, B. Soft-palate electrodes, and C. Orbit electrodes. The soft-palate electrodes are integrated into a mouth-guard like device that the patient bites down on which reduces the possibility of choking on the device and secures the electrodes to the roof of the mouth. Self-adhesive standard EEG electrodes may be used as alternatives for the soft palate if the patient shows discomfort to the rigid lattice. All electrodes will be safely secured outside of the mouth and closely monitored to reduce the possibility of choking.

[a] Kahraman A, Hilsenbeck J, Nyga M, et al. Bioelectrical impedance analysis in clinical practice: implications for hepatitis C therapy BIA and hepatitis C. *Virol J*. 2010;7:191. Published 2010 Aug 16. doi:10.1186/1743-422X-7-191
[b] Putensen C, Hentze B, Muenster S, Muders T. Electrical Impedance Tomography for Cardio-Pulmonary Monitoring. *J Clin Med*. 2019;8(8):1176. Published 2019 Aug 7. doi:10.3390/jcm8081176
[c] Cho Kye Hee, Han Eun Young, Lee Seung Ah, Park Hyun, Lee Chan, IM Sang Hee. Feasibility of Bioimpedance Analysis to Assess the Outcome of Complex Decongestive Therapy in Cancer Treatment-Related Lymphedema. *Frontiers in Oncology*. Vol 10, 2020. Doi: 10.3389/fonc.2020.00111.
[d] Seoane F, Reza Atefi S, Tomner J, Kostulas K, Lindecrantz K. Electrical Bioimpedance Spectroscopy on Acute Unilateral Stroke Patients: Initial Observations regarding Differences between Sides. Biomed Res Int. 2015;2015:613247. doi:10.1155/2015/613247
[e] S. Khan, P. Manwaring, A. Borsic, and R. Halter, "FPGA-Based Voltage and Current Dual Drive System for High Frame Rate Electrical Impedance Tomography," IEEE Trans. Med. Imaging, vol. 34, no. 4, pp. 888–901, 2015.
[f] R. J. Halter *et al*., "Real-Time Electrical Impedance Variations in Women With and Without Breast Cancer," in *IEEE Transactions on Medical Imaging*, vol. 34, no. 1, pp. 38-48, Jan. 2015, doi: 10.1109/TMI.2014.2342719.

4. Analysis

Describe any qualitative tests and measures as well as quantitative methods:

hdEEG Processing
Pre-processing of EEG data will be performed using Net Station 5 (Electrical Geodesics Inc., Eugene, Oregon). The coordinates of each electrode will be corrected for each patient based on the pictures taken by the geodesic dome preceding the EEG recording. Artifact detection will be performed to mark all EEG segments containing eye and head movement or muscle artifacts. The EEG data will be band-pass filtered between 0.5 and 70 Hz. T1 MRI images for each patient will be segmented using FreeSurfer and imported into
Brainstorm, a Matlab-based program dedicated to EEG data analysis. In Brainstorm, a head model will be created and each patient's electrode coordinates will be imported/co-registered with the T1 MRI images.

EEG data will be exported and pre-processed by Matlab programs developed in-house. The global field potential (GFP) and entropy across all 256 or 128 channels will be computed at each time point. GFP is sensitive to polarity changes across channels, while entropy could be helpful to eliminate EMG artifacts. Interictal epileptiform discharges (IEDs) will be identified by auto-thresholding both GFP and entropy. The source localization of IEDs will be determined using inverse solutions in Brainstorm. If applicable, intracranial EEG and/or intraoperative ECoG recordings will be used to evaluate the accuracy of IED source localizations. In addition to the self-developed detection algorithm, we will also utilize Spike Beacon software, which is developed by EGI to detect interictal discharges and compare it with our own algorithms.

For each subject, the EEG signals will be analyzed in 84 regions of interest (ROIs) defined according to the 42 Brodmann areas (BAs) for the left and right hemispheres. These ROIs will be defined for each subject using FreeSurfer. Low resolution electromagnetic tomographic analysis (LORETA) will be used to inversely estimate the EEG signal from these ROIs to localize cortical and subcortical sources from EEG signal generators. The EEG data will be investigated in the following aspects: 1) frequency content, including relative composition of delta (0.5-3 Hz), theta (3-7 Hz), alpha (7-13 Hz), beta (13-30 Hz), and gamma (>30 Hz) EEG oscillations along with their percent ratios; and 2) spatial heterogeneity, including global functional connectivity and interhemispheric asymmetry in the above-mentioned frequency bands.

For patients with peripheral nerve dysfunction, we will compare the amplitude and latency of the SSEP responses, and the source localization on individual brains between pre- and post-operative visits.

Stroke hdEEG-, EIT-, and EIS-based analysis
The aim of the hdEEG, EIT, and EIS analyses is to investigate how well these technologies function alone or in combination with each other or with other information, such as the NIHSS, CT or MRI-images to aid in 1) discriminating hemorrhagic from ischemic stroke, 2) monitoring of stroke patients, and 3) predicting stroke outcomes.

hdEEG. The stroke hdEEG-processing will follow the steps as outlined above. In particular to stroke, we will additionally 1) perform spectral analysis to identify regions with EEG slowing (i.e., stroke region(s)), 2) use SSEP to assess sensorimotor function, and 3) investigate a novel algorithm, called EEG-No Source Imaging (NSI), which aims to localize the stroke through a hypothesis testing approach.

EIT. The collected EIT data will be used to construct 3D images of electrical properties within the head using single- and multi-frequency image reconstruction approaches. The reconstructions rely on a 3D tetrahedral mesh of the domain; nominal and patient-specific meshes will be considered. We will utilize the FreeSurfer-segmented data for this effort. We will consider reconstructions with and without structural information, e.g. skull, CSF, and stroke boundaries. Algorithms will also be considered that incorporate both EEG and EIT information. Electrical properties of the stroke, penumbra, and other ROIs will be considered for analysis.

EIS. The EIS data will look at raw impedance magnitudes and spectral properties of the acquired multi-frequency traces. Phase, magnitude, resistance, reactance and spectral fitting metrics will all be extracted

from the signals and explored in the development of a novel algorithm to isolate an intracranial abnormality, e.g., stroke region(s). This processing will include analysis of the heterogeneity of the surface potentials and will be compared to prior patient imaging to test the ability to detect, identify and localize stroke. Data will be explored in three cohorts: 1) all stroke vs all healthy 2) all ischemic vs all hemorrhagic and 3) large vs small infarct. Potential augmentation of EIS signals with EIT or EEG traces will be explored as well.

Statistical Analyses. Metrics from EEG, EIT, and EIS analyses will be used for structural and functional assessment. **Structural:** We will use Receiver-Operator Characteristic (ROC) curve analysis to produce clinical metrics (area under the curve, true and false positive rates, true and false negative rates, sensitivity, specificity, positive predictive value, negative predictive value, accuracy, etc.) for the detection testing (discriminating stroke type). Accuracy (position errors) will be used to assess stroke localization. Linear regression will be used to correlate metrics/electrical properties with volume and R^2 and p-values will define the goodness of fit. **Functional:** We will explicitly evaluate linear and multi-parameter regression models as part of our analysis (including correlation, p-values, and standard deviations of residuals). Comparisons will be made between hdEEG, EIT, and EIS techniques and SSEP metrics to determine which provides the most information or if they provide complementary information through multiple linear regression and/or analysis of variance (ANOVA).

5. Study Progress Monitoring

Note: appropriate monitoring may include periodic assessment of the following:

- data quality
- timelines
- recruitment and enrollment

Provide a description of the methods which will be used to determine the progress of the study, including periodic assessments of data quality, timelines, recruitment, and enrollment as appropriate:

The PI and co-investigators will periodically review progress of the experimental testing, including assessments of data quality, patient recruitment, and progress toward validation of test effectiveness. Adverse reactions or problems with the testing performed at DHMC or reported by others will be addressed immediately and reported to the Dartmouth-Hitchcock Health Institutional Review Board (D-HH IRB).

6. Risks & Benefits

Note: Risks may be physical, psychological, social, legal, economic, to reputation, or others.

a. Describe any potential risks, their likelihood and seriousness:

This study will not create additional risk to patients with neurological disorders due to the hdEEG recording, and may result in only minimal risk associated with electrical impedance measurements.

hdEEG
High-density EEG does not disrupt or prolong ongoing testing of the patient. Patients will be on full doses of medications during the short-term study. For patients enrolled in the long-term study, their anti-seizure medication, if appropriate, will be decided by their attending neurologists or neurosurgeons. Patient confidentiality will be strictly protected.

Electrical Impedance Measurements

The risks associated with the EIT/EIS data collection to be used are minimal. Two previous CPHS-approved protocols (CPHS #12832 and #16798) have been in place for approximately 10 years for imaging the breasts of women (>200) with screening abnormalities (via external surface measurements) and for in vivo probing of breast tumor tissue during surgery with a needle-based impedance sensing probe (i.e. internal impedance measurements) without incident. Risks are the following 1) the potential malfunctions of the EIT/EIS systems which could result in the application of mild currents to the subject, and 2) potential gagging or choking on the soft-palate electrode mouthpiece. All patients will be closely monitored for any potential breathing or other difficulties during testing, and the test will be paused or stopped if this occurs. Electrical impedance testing uses electromagnetic energies at very low (non-perceptible) levels that, to the best of current scientific knowledge and experience, do not cause either short or long-term health effects. At higher powers, these energy sources can damage tissue through thermal processes. In the extreme, it may be possible to generate enough focal energy deposition to cause a blister on the skin (or tissue) surface. These risks could cause an injury that would require an outpatient visit (possibly with follow-up) and perhaps prescription of a topical medication for promotion of wound healing. However, because of the protections put in place (discussed below), all of these potential risks are extremely unlikely to occur.

Optical Scanners

Every effort will be made to protect patient privacy. All scans will immediately be transferred to approved research computers and original scans on the research-only iPhone/iPad will be deleted. Secondary checks will be performed on the scans and if any identifiable information remains in the scans they will be removed.

Subject Tasks

Subjects may experience discomfort when they are asked to view certain pictures or be engaged in certain tasks (for instance, viewing IAPS pictures).

Evoked Potentials

Subjects may experience discomfort when their peripheral nerves are stimulated to trigger evoked potentials in their cerebral somatosensory areas. They will feel some involuntary twitching sensations of their fingers or toes.

Non-Significant Risk Device Overview:

The owner and developer of the device is the Thayer School of Engineering at Dartmouth.

EIT system. For this study we will use one of two EIT systems; 1) a custom-designed 20-channel EIT system (Fig. 1D) or 2) a 32-channel commercial Sciospec (Bennewitz, Germany) EIT system. Each system is broadband being able to measure from 100 Hz to 1 MHz. System 1's specifications are detailed in [29], which include SNR > 90 dB that possesses high speed capabilities (up to 80 frames/ second (fps)) [a]. System is flexible and has a modular hardware and software design that allows for performance upgrades such as DAQ frame rate and SNR, andit uses National Instruments (NI) hardware and software modules, which offer inherent compatibility over generations of hardware and software revisions. System 2 can easily switch between high speed acquisition (up 100 frames/second) or slower multifrequency acquisition. Manual multiplexing allows data to be recorded from 120 electrodes (20 at a time for System 1 or 30 at a time for System 2). Each system is connected through an isolation transformer to protect the patient from any power surges and complies with International Electrotechnical Commission (IEC) requirements for safety and essential performance of medical electrical equipment (IEC 60601-1).

EIS system. For this study we will use a custom-designed EIS system. It is a broadband (100 Hz-500 kHz) 30-channel DAQ system with a SNR > 80 dB that possesses high speed capabilities (50 fps). The system uses NI hardware and software modules, switching capabilities and will be connected through an isolation transformer to further protect the patient from any power surges.

Similar systems have been implemented previously (see above) and the system complies with International Electrotechnical Commission (IEC) requirements for safety and essential performance of medical electrical equipment (IEC 60601-1).

a. S. Khan, P. Manwaring, A. Borsic, and R. Halter, "FPGA-Based Voltage and Current Dual Drive System for High Frame Rate Electrical Impedance Tomography," *IEEE Trans. Med. Imaging*, vol. 34, no. 4, pp. 888–901, 2015.

b. Confirm that risks to subjects have been minimized, by use of procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk:

We will use standardized tasks in this study. For example, the IAPS (International Affective Picture System) is developed to provide a set of standardized emotional stimuli for experimental investigations of emotion and attention. The participants will be asked to rate how pleasant/unpleasant they feel when looking at each picture. These pictures have been used in many studies related to emotion and attention.

Prior to starting the task, each patient or control subject will be warned about the nature of the task (e.g., IAPS pictures). If the patient or control subject feels that the task is not appropriate, they will be able to terminate the task at any point.

Peripheral nerve stimulation will be triggered with minimum current for each individual. If the subject cannot tolerate the induced twitching or sensation, they will be able to terminate the task at any point.

EIT/EIS Measurement
System Malfunction: The electrical impedance measurement systems adhere to accepted safety standards. All of the instrumentation that has been (or will be) developed and that is currently in use operates below the accepted safety standards [IEEE Standards for Safety Levels with Respect to Human Exposure to Radio Frequency Electromagnetic Fields, 3KHz to 300 GHz, 1992]. Every step will be taken to prevent the exposure of any subject to higher than allowable currents, i.e. double isolation from the alternating-current (AC) main through the use of isolation transformers, use of direct-current (DC) blocking capacitors on every analog line in contact with the subject, and software limiting the current to allowable levels. These multiple levels of protection are standard practice for the use of medical equipment in contact with subjects and have proved in the past to be very safe.

Risk of choking: The developed mouthpiece (sterile lattice, Fig. 1B) is designed to conform to the subjects' mouth and can be bit down on, reducing chances of choking. For the alternative standard Ag/AgCl electrode approach each electrode will be tethered outside the mouth at a patient-specific length, reducing chances of choking/swallowing. Furthermore, data recording from these electrodes will be limited to 3-minute windows at the beginning and end of the ~30 minute recording sessions during which time investigators will be closely monitoring the subjects, ensuring that they remain safe.

c. Describe why all the risks to subjects are reasonable in relation to both anticipated benefits and the knowledge expected to be gained from the study:

hdEEG
The cognitive task is designed to investigate the participants' emotion, cognition and attention. The discomfort they may experience will reflect the changes in their emotion, cognition and attention, which is essential in our investigation.

The functional tasks (motor and sensory) are designed to map the subjects' primary motor and somatosensory brain areas. Peripheral nerve stimulation can reliably trigger a robust response in subjects' somatosensory areas. And this protocol has been clinically used both for outpatient neurodiagnostic tests and inpatient intraoperative neuromonitoring purposes. Detailed mapping of the subjects' primary motor and somatosensory areas are very important for certain types of surgical intervention, such as resection or neurostimulator implantation in epilepsy patients.

EIT/EIS
Stroke affects hundreds of thousands of unfortunate victims on a yearly basis and improvements in stroke detection, monitoring, and prognostication could have a significant impact on patient care. The data collected here will represent an important step in determining the potential for EIT/EIS or their combination with MRI/CT and hdEEG and/or MRI/CT for these applications.

7. Unexpected Events or Incidental Findings

Note: It may be important to consider the potential for certain unanticipated events to occur, for example:
- finding an anomaly in a MRI
- discovering child abuse
- causing distress in interviews of a sensitive nature

Describe potential events and provide a plan of action:

In the unlikely event that patients experience a seizure during the study, DHMC staff neurologists/epileptologists (K. Bujarski and E. Kobylarz) will be on site to provide immediate care.

8. Placebo Use or Inconsistency with Standard of Care

Does any part of this study involve the use of a placebo or procedures that are inconsistent with the standard of care at Dartmouth-Hitchcock Medical Center?

☒ **No** ☐ **Yes**

If Yes, explain how the use of placebo or non-standard of care therapy may affect risks for participants, addressing the following:
- The safety and efficacy of other available therapies
- The maximum total length of time a participant may receive placebo on study
- The greatest potential harm that may result from not receiving or delaying effective therapy
- Safeguards for the participants receiving placebo or non-standard of care therapy

9. Genetics

Does any part of the study involve genetic analysis of biological specimens?

☒ **No**

☐ **Yes,** the study is based on the premise that a link between a genotype or a biomarker and a specific disease or condition is clinically useful in predicting the development of that specific disease or condition.

Please complete the Genetic Research Form and upload it to the 'Supporting Documents' page in Rapport.

-OR -

☐ **Yes,** the study is looking for an association between a genotype or a biomarker and a specific disease or condition, but at this point it is not clear if the genetic marker has predictive value. The uncertainty regarding the predictive value of the genetic marker is such that studies in this category will not involve referral of participants to genetic counseling; however, participants will be informed of genetic testing in the consent form. **Please comment:**

10. Equitable Participant Selection

a. Estimated number of participants at Dartmouth CPHS reviewed sites:

For the short-term hdEEG study: 100 epilepsy patients, 15-20 brain tumor patients and 15-20 normal controls. For the short-term stroke study: 50 EIT/EIS-measured patients with 50 controls. For the long-term study: 20 epilepsy patients. For the peripheral nerve study: 20 subjects.

b. Provide a justification of the proposed sample size

After completing pilot studies, we will focus on those tests which appear to be elicit consistent, localized brain activation. Under these circumstances adequate statistical power should be obtained by repeating these tests in 15-20 patients. However, for the short-term epilepsy study we are more interested in investigating the correlation between the spike localizations and other clinical diagnostic results. Due to their very deep location, the determination of spike localization could be challenging in some epilepsy patients. In order to have a better understanding of the efficacy of using high-density EEG to provide useful information for various types of epilepsy patients (i.e., temporal vs. extra-temporal), we would like to perform this study on a larger patient size.

For the EIT/EIS cohort, sample size is based on previous contrasts observed in ex-vivo ischemic and hemorrhagic tissue [a]; specifically, the conductivities at 1 kHz were 0.075 Siemens/meter (S/m) for hemorrhagic tissue and 0.11 S/m for ischemic tissue. For a reported standard deviation of 0.025 S/m, there would be a 95% power to detect significant differences through an unpaired t-test with a group sample size of ten subjects for each cohort (20 total). An initial investigation into non-invasive in-vivo signals results in an ~50% drop in signal, requiring a 2x increase in sample size and a total desired cohort of n=50, split into two sub-cohorts of n=25 ischemic and hemorrhagic stroke, respectively. However, as this is a pilot study, these are projections; should initial data indicate higher signal contrast and lower standard deviations than anticipated, the numbers will be revisited to ensure optimized patient recruitment.

[a] Yang, L., Zhang, G., Song, J., Dai, M., Xu, C., Dong, X., & Fu, F. (2016). Ex-Vivo Characterization of Bioimpedance Spectroscopy of Normal, Ischemic and Hemorrhagic Rabbit Brain Tissue at Frequencies from 10 Hz to 1 MHz. *Sensors (Basel, Switzerland)*, *16*(11).

c. Define the target population:

☐ **Epilepsy patients**

Patients with a diagnosis of epilepsy will be considered for participation if they are interested and in the judgment of the research team they require further mapping or are capable of performing the functional and/or cognitive tasks required of the study.

Inclusion criteria:
1. Able to perform the tasks
2. Subject or legally authorized representative able to provide appropriate consent

Exclusion criteria:
1. Subject or legally authorized representative unable to provide consent
2. Additional neurologic or psychiatric diagnosis such as stroke, tumor, or psychosis judged to interfere with high-density EEG.

□ **Brain tumor (lesion) patients**

Patients with diagnosis of brain tumor (lesion) will be considered for participation if they are interested and in the judgment of the research team they require further mapping or are capable of performing the functional and/or cognitive tasks required of the study.

Inclusion criteria:
1. Able to perform the tasks
2. Subject or legally authorized representative able to provide appropriate consent

Exclusion criteria:
1. Subject or legally authorized representative unable to provide consent
2. Additional neurologic or psychiatric diagnosis such as stroke, or psychosis judged to interfere with high-density EEG.

□ **Peripheral nerve dysfunction patients**

Patients with diagnosis of peripheral nerve dysfunction who would benefit from surgical repair/graft/transfer procedures will be considered for participation if they are interested and in the judgment of the research team they require further mapping or are capable of performing the functional and/or cognitive tasks required of the study.

Inclusion criteria:
1. Able to perform the tasks
2. Subject or legally authorized representative able to provide appropriate consent

Exclusion criteria:
1. Subject or legally authorized representative unable to provide consent
2. Additional neurologic or psychiatric diagnosis such as brain tumor, stroke, or psychosis judged to interfere with dense array EEG.

□ **Stroke patients**

Patients with acute stroke who have been stabilized will be considered for participation if they are interested.

Inclusion criteria:
1. Able to perform the tasks
2. Subject or legally authorized representative able to provide appropriate consent

Exclusion criteria:
1. Subject or legally authorized representative unable to provide consent
2. Additional neurologic or psychiatric diagnosis such as brain tumor, epilepsy, or psychosis judged to interfere with dense array EEG.
3. Subject unable to show signs of distress
4. Persons who are pregnant.

☐ **Normal Controls**

Age, gender, and education matched normal controls will be recruited using community messaging boards and advertisements.

Inclusion criteria:
1. Able to perform tasks
2. Able to provide their own consent
3. Matched in age, gender, and educational level to the patient population

Exclusion
1. Unable to provide consent
2. Additional neurologic or psychiatric diagnosis such as stroke, tumor, epilepsy, or psychosis.

☐ Gender and Racial/Ethnic distribution

Over the past years, roughly equal numbers of male and female patients have been treated by the DHMC Epilepsy Program. The racial/ethnic distribution of our patient population reflects that of our Northern New England referral base, which is primarily Caucasian with small numbers of Asians, African-Americans and Hispanics. This may shift somewhat in the future with the DHMC Epilepsy Program's outreach activities and recruitment of patients from other locales.

d. Vulnerable populations

Note: Certain populations are considered vulnerable to coercion and undue influence and are provided with additional protections when participating in a research study.

Identify any of the below populations which you plan to recruit for this study. In addition, complete the form(s) linked with each population as necessary and upload on the 'Supporting Documents' page in Rapport.

☐ Pregnant Women, Fetuses and Neonates

☐ Children

☒ People with impaired decision-making capacity

The following populations may also be considered vulnerable to coercion or other undue influence:

- Prisoners
- People who are economically disadvantaged
- The elderly
- People who are illiterate or do not speak English
- Students and employees

Describe any other potentially vulnerable population(s) and the additional protections provided to them:

Because neurological disorders (stroke, tumors, peripheral nerve damage, or epilepsy) can happen to anyone, regardless of race, age, sex, place of study or work, it is possible that people who are economically disadvantaged, elderly, or students or employees of Dartmouth/Dartmouth Hitchcock Medical Center might be eligible for this trial. We will not be specifically recruiting these populations, and all eligible participants will be treated in the same manner without coercion or undue influence.

It is possible that some eligible participants will have cognitive issues related to their neurological condition. If this is the case, a legally authorized representative (LAR) will be asked to consent for the subject. In cases where an LAR is appropriate, stroke patients will still be involved in the consent process as much as possible.

Because of the added electrodes in the EIT/EIS system, we will take extra precautions to make sure that stroke patients are able to express discomfort. Most stroke patients, even if non-verbal, are able to display signs of understanding or distress (nodding, grimacing, etc). All stroke patients will be evaluated by providers for conditions that might preclude them from showing signs of distress or discomfort, and these patients will be excluded from the study. Additionally, stroke patients will be closely monitored throughout the procedure for any non-verbal/physiological signs of distress.

It is possible that some participants could be illiterate. If this is the case, they can make their mark on the ICF, and it will be countersigned by an impartial witness or LAR. In all cases, the PI or sub-investigators will make the determination that the participant has the ability to understand and/ or comply with the study procedures.

11. Recruitment

Describe method(s) of recruitment. Associated advertisements and other materials to be used for recruitment should be uploaded to the 'Consent Forms and Recruitment Materials' page in Rapport.

Patients will be recruited from the Section of Neurosurgery by Dr. Linton T. Evans and Jennifer Hong, Department of Neurology by Dr. Diana Rojas-Soto, Dr. Erik Kobylarz, Dr. Timothy Lukovits and associate providers, inpatient Epilepsy Monitoring Unit or the outpatient epilepsy center staffed by Dr. Krzysztof Bujarski. Written informed consent will be obtained. The PI or designee will seek to obtain Informed Consent after consulting with the attending neurologist, who will decide if and when testing is advisable in each patient. Normal controls will be recruited using community messaging boards and advertisements. A normal consent form will be used for normal controls.

12. Informed Consent, Assent, and Authorization

All forms discussed in this section should be uploaded to the 'Consent Forms and Recruitment Materials' page in Rapport

a. Please describe the consent and/or assent process, addressing the following:

- Who will obtain consent/assent from participants
- Where the consent/assent process will take place
- The timeframe for providing information potential participants about a study, having the consent form signed, and beginning study activities
- Any precautions taken to minimize the possibility of coercion or undue influence

- The forms which will be used as well as any aids used to simplify scientific or technical information
- How comprehension will be ensured

Consent for this study will be obtained by Dr. Krzysztof Bujarski, Dr. Erik J. Kobylarz, Dr. Linton T. Evans, Dr. Jennifer Hong, Dr. Joshua P. Aronson, Dr. Diana Rojas-Soto, Dr. Timothy Lukovits, Dr. Barbara C. Jobst, or other designated study team members either in the outpatient EEG lab or in an inpatient Neurology Unit. The initial recordings will be done within a day to a week following obtaining the consent. The procedure will be explained to the patient in detail.

If the subject is determined to have cognitive issues due to a stroke or other impairment, an LAR will be present during the consent process. All subjects, including subjects that need LAR, will be involved in the consent process and every effort will be made to include them in the conversation to the extent of their ability.

b. Waiver(s) or alteration(s) may be requested for research that involves no more than minimal risk.
Indicate requested waiver(s) or alteration(s) below. In addition, complete the corresponding section of the Waivers and Alterations Request Form and upload it to the 'Consent Forms and Recruitment Materials' page in Rapport.

- ☐ For the informed consent *process*
- ☐ For the *documentation* of informed consent
- ☐ For the HIPAA Authorization to use and/or disclose PHI
- ☐ For a waiver of the requirement for medical record documentation

13. Financial impact on participants

a. List the tests, visits, and procedures performed for only research purposes and specify who will pay:

Note: Research procedures may not be billed to a health insurance plan

The high-density EEG and the EIT/EIS procedures will not be billed to any health insurance plan. For outpatients, we will try to schedule their visits on the same day when the patient is having MRI/PET/SPECT or imaging studies or on their last day of EMU admission for their convenience.

14. Compensation or Gifts

Please describe any payments, gifts or reimbursements participants will receive for taking part in the study:

EEG and epilepsy subjects will not be compensated.

Stroke study patients will be compensated $25 for enrolling in the study.

15. Privacy of Participants

Note: Methods used to obtain information about participants may have an effect on privacy. For example:

- Consent discussions or interviews held in public which concern sensitive subjects or behaviors
- Observations of behavior, especially illicit behavior, in quasi-public settings

Describe any activities or interactions which could lead to a breach of privacy and provide a plan to protect participant privacy:

Consent discussions and interviews will be held in the doctor's office or patient's room to avoid any breach of privacy. The hdEEG recording will take place in the EEG laboratory on Level 3 or in the patient's room.

16. Confidentiality of Data

Note: Any person engaged in research collecting information that could cause financial, social or legal harm to participants may apply for a Certificate of Confidentiality. Certificates of Confidentiality are issued by the National Institutes of Health (NIH) to protect identifiable research information from forced disclosure. They are intended to allow the investigator and others who have access to research records to refuse to disclose identifying information on research participants in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level.

a. If disclosed, could any of the data collected be considered sensitive, with the potential to damage financial standing, employability, insurability, or reputation?

☒ **No** ☐ **Yes**

If Yes, describe the data or information, the rationale for their collection, and whether a Certificate of Confidentiality will be obtained:

b. Describe the safeguards employed to secure, share, and maintain data during the study, addressing any of the following which may apply:

- Administrative, ie. coding of participant data
- Physical, ie. use of locked file cabinets
- Technical, ie. encrypted data systems

All data in this study will be referenced to a study participant number, which will be different from any of the identifying numbers used by the participating hospital or by the participants' insurer. All electronic data will exclude participants' names, addresses, social security numbers or other identifiers.

All data will be kept on a HIPAA-compliant secure servers at Dartmouth-Hitchcock Medical Center and the Thayer School of Engineering. Access will be restricted by a user/password system and limited to the investigators working on this study. Source data files will include EIT data. Source data will be retained for a minimum of three (3) years. All physical data (paper or backup discs) will be kept in locked research offices at Dartmouth-Hitchcock Medical Center and the Thayer School of Engineering lab located at DHMC.

Upon study conclusion, identifiers will be maintained for at least 3 years, after which they will be destroyed. All paper-based identifier data will be shredded and discarded in the usual manner. All electronic identifier data will be erased from the servers. Physical data will be destroyed as appropriate (discs will be shredded).

c. Describe the plan for storage or destruction of data upon study completion:

All of the de-identified data will be stored on DH and Thayer School of Engineering managed computers upon study completion.