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D-HH IRB OVERSIGHT:

One of the following must be true in order to submit to the D-HH IRB. Please check all that apply:

☒ The Principal Investigator is employed by D-H
☒ The study will utilize any D-H data or specimens
☒ The study will enroll D-H patients or recruit from D-H sites
☒ The study will utilize any D-H resources, e.g. study procedures will occur at D-H locations and/or use of D-H equipment or shared resources

PROTOCOL TITLE:

Modulation of emotion perception in humans via amygdala stimulation

PRINCIPAL INVESTIGATOR:

Krzysztof A. Bujarski
Department of Neurology
Telephone Number 603-650-5000
Email Address Krzysztof.A.Bujarski@hitchcock.org

PROTOCOL TITLE: Neuromodulation of affective valence in humans by amygdala stimulation

VERSION NUMBER/DATE:

V5.0_12Sep2023

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
V2.0	25Jul2022	The Differential Emotions Scale was not providing us with data required for this study. Instead, it was decided to use The Emotion Self-Rating Scale (ESR) that would be more appropriate to gather needed information	Yes
V3.0	17Oct2022	1. Section 14.0: added language to allow participants to continue their participation in the testing sessions on the same day even if they experience a single clinical seizure. The PI or other study personnel delegated this task will make the final determination. 2. P.15: language added to reflect:" The scale will be administered electronically (on the testing computer). 3. P.16: Updated Study Timelines 4. Minor edits and formatting changes throughout the entire document.	Yes
V3.1	16Nov2022	Section 15.0: added language related to AEs	Yes
V4.0	21Apr2023	Section7.0: Data and Specimen Banking Section 17.0: Data Management and Confidentiality Section 24.0: HIPPA Authorization Waiver	No
V5.0	12Sep2023	Section6.0: Procedures involved. Clarification added in inclusion criteria Section 9.0: Study Timeline- enrollment up to January 1, 2024, data analysis January 2, 2024-January 1, 2025 Section 10.0: Inclusion/Exclusion Criteria: • "FSIQ 75 and above or any equivalent test of generalized intelligence as	No

		determined by the PI to adequately predict engagement in the task"	
V6.0	28Nov2023	Section 5.0: Adding clarification about the Blackrock stimulator	No

Table of Contents

1.0 Study Summary

Study Title	Modulation of emotion perception in humans via amygdala stimulation
Study Design	Experimental
Primary Objective	To determine if electrical stimulation targeted to specific sub-nuclei of the amygdala can induce a change in perception of affective valence.
Secondary Objective(s)	1. To have a clear understanding of the safety and efficacy of our targeting and stimulation parameters on cognition and induction of undesired side effects. 2. To determine if the human amygdala can be a suitable DBS target to treat psychiatric disorders known to involve the amygdala.
Research Intervention(s)/ Investigational Agent(s)	We will use clinically accepted and safe methods to understand the effects of amygdala stimulation on side effects and induction of electrographic discharges.
IND/IDE #	N/A
Study Population	Patients (18 years or older with normal cognition and fit all inclusion and exclusion criteria) who have intracranial EEG electrodes for evaluation of candidacy for epilepsy surgery.
Sample Size	16 intracranial EEG patients
Study Duration for individual participants	Approximately 2 – 3 weeks
Study Specific Abbreviations/ Definitions	AIC – Advanced Imaging Center BLN – Basolateral Nucleus CN – Centromedian Nucleus DBS – Deep-Brain Stimulation DHMC – Dartmouth-Hitchcock Medical Center EBS – Electrical Brain Stimulation EEG - Electroencephalogram EMU - Epilepsy Monitoring Unit ESR- The Emotion Self-Rating Scale GAD – Generalized Anxiety Disorder IAPS – International Affective Picture System ISM – Independent Safety Monitor MHMH – Mary Hitchcock Medical Hospital MPI – Message Passing Interface OASIS – Open Affective Standardized Image Set PTSD – Post-Traumatic Stress Disorder

2.0 Objectives

The main objective of this study is to investigate how the amygdala processes affective valence and to determine if electrical stimulation targeted to specific sub-nuclei of the amygdala can be safely used to induce a change in perception of affective valence. Our central hypothesis is that electrical stimulation of the basolateral nuclear group (BLN) of the amygdala during performance of an affective valence perception task will change how patients perceive affective valence in pictures without causing the undesirable side effects of stimulation. We propose that the induction of this effect on cognition will have future implications for the treatment of specific psychiatric disorders that are known to involve the amygdala.

Specific Aim 1. Characterize oscillations of the amygdala and its connections during judgment of valence. We will record intracranial electroencephalogram (EEG) oscillatory rhythms from the valence circuit, including the amygdala and, as available, the anterior insula, the dorsal anterior cingulate, and ventromedial prefrontal lobe during performance of the Affective Valence Perception Task. Our working hypothesis is that we will find activation and connectivity across the valence circuit, which will provide new insights into the representation of valence.

Specific Aim 2. Determine the effect of electrical stimulation targeted to the amygdala on safety and cognition

A. We will determine if stimulation, per new parameters and location, induces undesired effects or electrographic after-discharges. Our working hypothesis is that targeting the BLN of the amygdala and using parameters appropriate for long-term deep-brain stimulation (DBS) will not induce any undesired effects.

B. We will measure the effect of amygdala sub-nuclei stimulation on perception of affective valence. Our working hypothesis is that electrical stimulation of the BLN will change the perceived valence of the picture presented.

Research Hypothesis
We propose that neuromodulation of the valence circuit through electrical stimulation of the amygdala may have therapeutic implications in treatment-resistant psychiatric disorders, such as generalized anxiety disorder, post-traumatic stress disorder, and aggression. We believe that there is a critical need to investigate specific targets within the amygdala and to define stimulation parameters that will allow for safe neuromodulation of

the human amygdala using DBS. Without this knowledge, we will miss an opportunity to develop an effective intervention for many disabling psychiatric conditions.

3.0 Background

Studies show that the world-wide burden of psychiatric disease is immense (Whiteford, Ferrari et al. 2015, Rehm and Shield 2019). A 2016 study measuring global burden of disease points to 7% of all disability-adjusted life years lost to uncontrolled mental health disorders (Vigo, Thornicroft et al. 2016). Despite advances in pharmaceutical options and novel forms of psychotherapy, a large proportion of patients with psychiatric conditions do not adequately respond to standard treatment (Al-Harbi 2012). For persons with mental illness who have not benefited from conventional intervention, neuromodulation is an emerging treatment option (Altinay, Estemalik et al. 2015, Cleary, Ozpinar et al. 2015, Coenen, Amtage et al. 2015, Graat, Figee et al. 2017). Neuromodulation is a method used for the long-term alteration of pathologic neural circuits by targeted electrical stimulation, with the goal of improving psychiatric function. Neuromodulation can be accomplished using non-invasive techniques, such as transcranial magnetic stimulation, or alternatively by invasive techniques, such as deep-brain stimulation (DBS). Although the exact mechanisms of neuromodulation are uncertain, several theoretical explanations have been suggested, including downregulation of network activity through tonic depolarization of neurons, inhibition of network activity by altering the synapse, and resetting abnormal oscillatory activity (McIntyre, Savasta et al. 2004, Ashkan, Rogers et al. 2017).

Despite the successful use of DBS in many neurological disorders, recent clinical trials of DBS in psychiatry have shown limited benefits (Graat, Figee et al. 2017, Widge, Malone et al. 2018). Currently, the only FDA-approved application of DBS in psychiatry is for the treatment of obsessive-compulsive disorder (Altinay, Estemalik et al. 2015). In their 2019 review of DBS, Lozano at al. conclude that the main obstacles limiting the use of DBS in psychiatry include the invasive nature of the treatment and our relatively poor understanding of the underlying anatomy of neural networks involved in psychiatric disorders (Lozano, Lipsman et al. 2019). Despite its invasive nature, increasing experience with DBS surgical techniques have improved its safety (Deer, Lamer et al. 2017). Furthermore, advancements in functional imaging are providing a more complete understanding of the underlying neural networks involved in psychiatric disorders (Deckersbach, Dougherty et al. 2006).

One of the most extensively studied regions in the human brain with respect to anatomy and function is the amygdala (McDonald 1998, Murray 2007, Benarroch 2015, Janak and Tye 2015). A simplified model of the human amygdala connectivity is shown in Fig 1. Upstream afferent projections from cortical and subcortical regions flow into the basolateral nucleus (BLN). The BLN, in turn, projects to the hippocampus, the entorhinal cortex, and the centromedian nucleus (CN). The CN is the main source of efferent projections out of the amygdala mostly to the ventromedial pre-frontal cortex, the hypothalamus, and the brainstem.

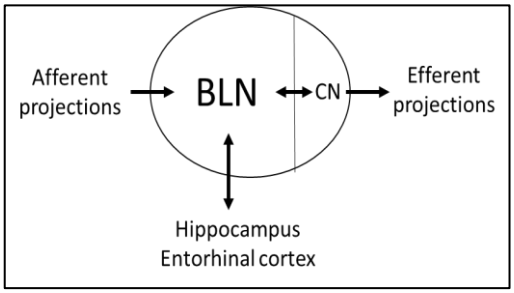

Fig 1. Model of the amygdala. BLN=basolateral nucleus; CN=central nucleus.

Extensive evidence from non-human and human animal studies implicate the amygdala in a wide variety of cognitive functions, including in affective valence and arousal (LaBar, Gatenby et al. 1998, Tye and Janak 2007, Fusar-Poli, Placentino et al. 2009, Salzman and Fusi 2010). Affective valence, or just valence, refers to the intrinsic attractiveness/"goodness" (positive valence) or aversiveness/"badness" (negative valence) of events, objects, or situations (Yee and Miller 1987, Garavan, Pendergrass et al. 2001, Lewis, Critchley et al. 2007, Ball, Derix et al. 2009, Salzman and Fusi 2010, Murray, Brosch et al. 2014). The National Institute of Mental Health Research Domain Criteria (RDoC) propose that affective valence is processed by a valence network which includes the BLN of the amygdala, the hippocampus, ventromedial prefrontal cortex, dorsal anterior cingulate cortex, the hypothalamus, and the insular cortex (Cuthbert and Insel 2013). The importance of the amygdala in representation of valence is evidenced by studies using functional imaging and in human patients with destructive amygdala lesions (Adolphs, Tranel et al. 1994, Hamann, Ely et al. 1999, Canli, Zhao et al. 2000, Anderson and Phelps 2001, Kilpatrick and Cahill 2003, Kensinger and Corkin 2004, Phelps 2004, Richardson, Strange et al. 2004, LaBar and Cabeza 2006, Sergerie, Lepage et al. 2006, O'Neill, Gore et al. 2018). Arousal, on the other hand, refers to the psychological state of wakeful attention and is important for detection of salience, or the relative importance and novelty of stimuli (LaBar and Cabeza 2006, Uddin 2017). Similar to valence, RDoC defines an arousal/salience circuit which includes the amygdala, insula, cingulate, and basal forebrain (Cuthbert and Insel 2013, Uddin 2017).

Mounting evidence from functional imaging studies shows that dysfunctional processing within the amygdala may be a common mechanism for a vast array of psychiatric illnesses, especially for post-traumatic stress disorder (PTSD) (Davey, Whittle et al. 2015, Dai and Jonnagaddala 2018). Models of PTSD propose that reduced top-down control by ventromedial prefrontal cortex leads to hyperactivity of the amygdala (Besnard and Sahay 2016). Among other things, this manifests clinically in patients as dysregulated valence processing of environmental stimuli (Wolf, Miller et al. 2009). Indeed, studies of valence processing in patients with PTSD correlate exaggerated activation of the amygdala to negatively valenced stimuli with increasing PTSD symptom severity, and decrease in activation with symptom improvement (Pissiota, Frans et al. 2002, Protopopescu, Pan et al. 2005, Shin, Wright et al. 2005, Francati, Vermetten et al. 2007).

An important source of evidence for the function of the human amygdala has come from studies using intracranial EEG (Guillory and Bujarski 2014). Intracranial EEG is a diagnostic tool used to understand the source of seizures in patients with epilepsy and involves the recording of EEG via depth electrodes surgically implanted directly into neural structures. In addition to detecting seizures, epilepsy patients undergoing an intracranial EEG study can be voluntarily recruited to participate in research. Despite many limitations, intracranial EEG has significant advantages compared to non-invasive methods such as fMR and PET especially with regards to temporal resolution, i.e. milliseconds for intracranial EEG compared to seconds for fMR and minutes for PET (Guillory and Bujarski 2014). Intracranial EEG analysis methods such as event-related potentials, event-related changes in power at specific frequency ranges, and task-related network coherence have provided insights into amygdala function and amygdala connectivity to other brain regions (Halgren, Walter et al. 1978, Oya, Kawasaki et al. 2002, Krolak-Salmon, Henaff et al. 2004, Pourtois, Spinelli et al. 2010, Sato, Kochiyama et al. 2011, Bijanki, Kovach et al. 2014, Guillory and Bujarski 2014, Inman, Bijanki et al. 2018, Inman, Manns et al. 2018).

In addition to recording brain activity, intracranial EEG can be used to deliver electrical brain stimulation (EBS) for the clinical purpose of functional mapping and also for research purposes (Guillory and Bujarski 2014). For instance, the function of the hippocampus has been assessed by giving patients with intracranial EEG a memory task while EBS is safely delivered to the hippocampus (Jacobs, Miller et al. 2016). The effect of EBS on the brain depends on the choice of parameters for EBS and on the specifics of neural network anatomy (Guillory and Bujarski 2014, Lozano, Lipsman et al. 2019). It is generally thought that pulse width determines the size of the region affected by stimulation; amplitude to the strength of the effect; and frequency to activation or inhibition of the network (Lanteaume,

Khalfa et al. 2007, Lozano, Lipsman et al. 2019, Mohan, Watrous et al. 2020). Recent study of the effect of EBS parameters showed that stimulation frequencies between 100 and 200 Hz are most likely to cause inhibition of underlying brain tissue (Mohan, Watrous et al. 2020).

Preliminary Data/Pilot Studies

We conducted 2 pilot studies in 13 epilepsy patients with intracranial EEG electrodes to investigate the processing of valence in the amygdala and the effect of amygdala EBS on valence perception (Bujarski, 2019). Fig 2 shows the experimental set up. Fig 3 shows the design of the Valence Judgment Task, where 48 pictures from the International Affective Picture System (Bradley 2007) of varying valence are presented to the patient.

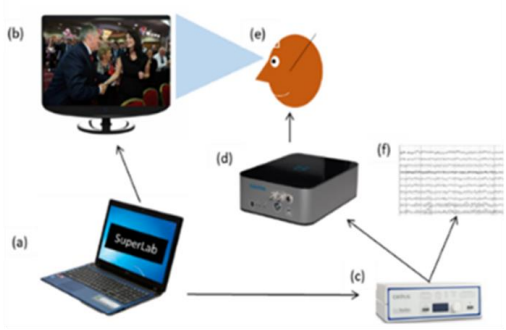

Fig 2. Experimental set-up. (a) Laptop computer running SuperLab is connected to 19'' monitor (b) which displays images. SuperLab is connected to Stimtracker (c) which triggers the Grass 12x stimulator (d) and places a marker on EEG (f). The patient (e) with intracranial EEG electrodes is watching the images and receives electrical stimulation.

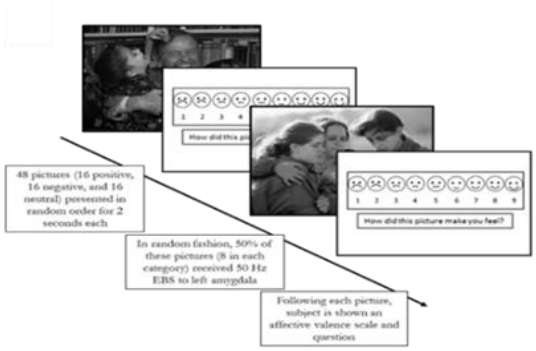

Fig 3. The Valence Judgment Task

Preliminary Study #1. We presented the Valence Judgment Task without EBS in 3 patients with electrodes in the left amygdala and obtained event-related potentials. We found activation of the amygdala to positively and negatively valenced pictures, and less so to neutral pictures approximately 500 ms following image presentation (Fig 4). These findings are consistent with numerous prior studies (Guillory and Bujarski 2014).

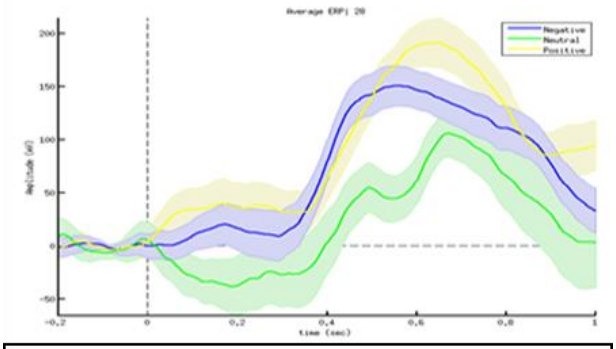

Fig 4. Event-related potential recorded from the left amygdala in The Valence Judgment Task

Preliminary Study #2: We presented the Valence Judgment Task with block-randomized EBS to 50% of trials in 10 patients with electrodes in the left amygdala. Fig 5 shows the location of electrodes in the left amygdala for all patients. Before administering the task, we determined the maximum safe EBS intensity for each patient by gradual increase from 1 mA to a goal of 5 mA or approximately 20 μC/cm^2, which is ~50% of maximum safe stimulation intensity.

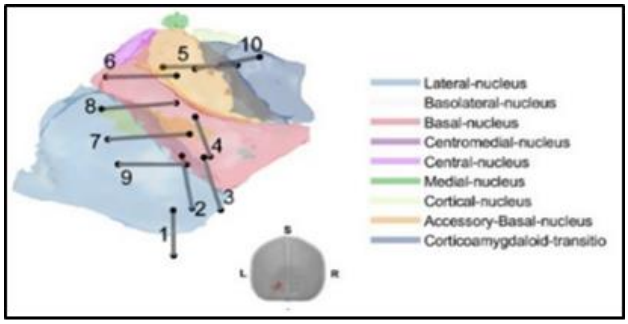

Figure 5. Location of electrodes within the amygdala.

We found that 9 of 10 patients eventually developed electrographic seizures related to EBS, 4 of which were associated with self-reported negative emotional symptoms. The average afterdischarge threshold was 3.4 mA (about 17μc/cm^2). This necessitated the incremental reduction of EBS intensity until no electrographic seizures and no subjective symptoms occurred. The average final stimulation intensity was 2.8 mA (12μc/cm^2). We subsequently administered the task. We found that amygdala EBS changed self-reported valence for negative pictures towards neutral (estimate 0.79, $p<0.01$), changed self-reported valence for positive pictures towards neutral (estimate -0.54, $p<0.05$), and did not change for neutral pictures (estimate 0.15, $p=0.58$). Fig 6 shows the effect of EBS for all 48 pictures averaged across all 10 patients.

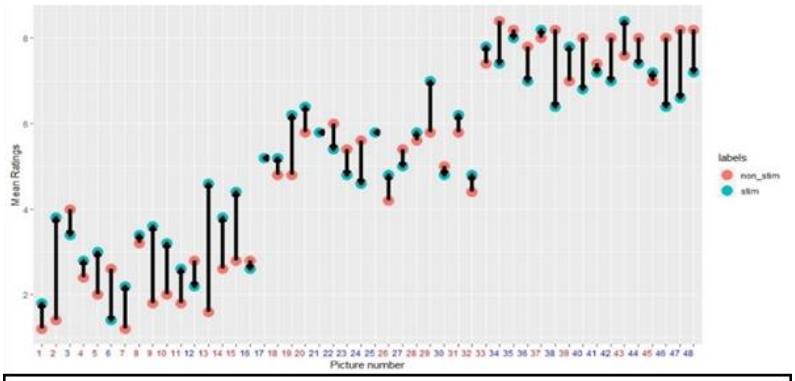

Fig 6. The effect of EBS on judgment of valence. X-axis shows valence rating for each of 48 images averaged across 10 patients for +EBS (blue) and –EBS (red) trials. Arrows show direction of change with EBS. Y-axis shows valence 1=negative 9=positive.

4.0 Study Endpoints

Anticipated Outcomes

We anticipate that task-related intracranial EEG recordings will lead to better understanding of neural circuits responsible for processing of valence.

- We expect to find increased power in the gamma band in the valence circuit (BLN > CN of amygdala).
- We expect to find increased coherence across the valence circuit with items of negative and (less so) positive valence.

We anticipate that targeting of stimulation to the BLN and the use of our suggested stimulation parameters will not result in any subjective sensations in the patient or electrographic after-discharges.

- We predict that we will produce effects on reported perception of valence for both positive and negative pictures without affecting neutral ones by stimulation of the BLN as opposed to the CN.
- We will randomize stimulation and analyze within patient effects of stimulation vs no stimulation.

Potential Pitfalls and Alternative Strategies

During an average year, 15 patients with refractory epilepsy are implanted with intracranial EEG electrodes at Dartmouth-Hitchcock.

- We believe that 16 patients will be an appropriate number that will fit the inclusion and exclusion criteria over period of two years that the study is conducted.
- If we cannot recruit 16 patients during this time, a no-cost extension for one year may be required.

If stimulation done by new parameters produces untoward side effects or does not replicate the cognitive change in valence seen in the preliminary study, we will change stimulation parameters. New parameters will modulate the frequency, amplitude, and pulse duration. These parameters will remain within clinically-determined safety limits. Additionally, parameters will be reviewed after each patient and changed incrementally, one at a time (see below). If it is determined that a change in stimulation parameters is needed outside of clinically-determined safe limits, a request will be formally submitted to the IRB.

- We will perform an effect-of-stimulation assessment after each patient. We may need to increase stimulation intensity, pulse duration, or change the location of stimulation. These changes will fall within clinically-determined safety limits: 10-200 Hz (Frequency), 0.1- 3 mA (Amplitude/Intensity), and 30-60 microseconds (Pulse duration).

- Any unexpected untoward effect of the stimulation will be assessed by the PI and reported to the Independent Safety Monitor (ISM) and IRB as required.
- Depending on the nature of the untoward effect, the stimulation parameters, the stimulation location, or the nature of the task will be adjusted.

5.0 Study Intervention/Investigational Agent

The main objective of this study is to determine if electrical stimulation of the human amygdala will modulate perception of valence and arousal. As such, our study intervention is electrical brain stimulation. To accomplish our objective, we will use a Blackrock system, specifically Blackrock stimulator that is able to deliver a wide range of EBS pulses (output voltage between 4.7-9.5 V, stimulation frequency 4 Hz to 5 kHz, pulse width 44 μs to 65535 μs, and maximum charge density of 20 μC/cm2) and fits well within the needed parameters.
This device is approved for human research. This device has been used extensively both in prior studies at Dartmouth-Hitchcock and other studies in epilepsy centers across the country. If safety concerns occur during the use of this device, such concerns will immediately be reported to PI, ISM, and IRB.

6.0 Procedures Involved

The study will be conducted in the inpatient Epilepsy Monitoring Unit at Dartmouth-Hitchcock Medical Center (DHMC) enrolling patients with epilepsy who are undergoing intracranial EEG for evaluation of possible epilepsy surgery. The study will be conducted in patients who do not have a specific psychiatric diagnosis, i.e. the aim is to use intracranial EEG in patients with epilepsy to understand amygdala electrophysiology and cognitive effect of EBS. The suitability of each patient for intracranial EEG is determined by a multidisciplinary board several months prior to the procedure. Only patients with appropriate electrode locations in the amygdala for clinical purposes will be identified during multidisciplinary epilepsy surgery conference and subsequently enrolled into the study. DHMC is a Level 4 Epilepsy Center with approximately 15 intracranial EEG patients per year. As such, we can estimate that we will enroll 16 study subjects over a 2-year funding duration. The task will be administered as patients are waiting for seizures to occur.

We will include patients 18 years or older with FSIQ 75 and above or any equivalent test of generalized intelligence as determined by the PI to adequately predict engagement in the task. All study procedures, including the range of emotional content in the images presented, will be reviewed, and participants will give independent consent for participation. We will exclude patients with any additional neurological disorders and/or psychiatric diseases that would limit their ability to provide informed consent and/or to perform study tasks within normal limits.

We will use the **Open Affective Standardized Image Set (OASIS)** for this study, as opposed to the International Affective Picture System (IAPS) used for the pilot (Bradley, 2007). The OASIS image set uses more contemporary images and is well validated. It is composed of 900 images that have standard rankings for valence based on a large normal control cohort. The images selected for the task vary with regards to valence (positive/neutral/negative) and arousal (low arousal/high arousal). For the task, all 900 images in the OASIS set were placed into one of the following four categories based on average valence and arousal ratings: Group 1: Negative Valence (<4) / Low Arousal (<4); Group 2: Negative Valence (<4) / High Arousal (>4); Group 3: Positive Valence (>4) / Low Arousal (<4); Group 4: Positive Valence (>4) / High Arousal (>4). From the 900 images of the entire OASIS set, 48 images were selected for each Group 1–4 for a total of 192 images. Average valence and arousal scores were calculated for each group and images were added and removed to optimize the two scores towards their respective extremes. Therefore, 192 images varying in arousal and valence were selected.

The task will be divided into Part 1 and Part 2.

- Part 1 will include 24 randomly chosen images from each of four categories (total of 96 images varying in valence and arousal) and will be presented without amygdala stimulation in Specific Aim 1 (see above).
- Part 2 will include 24 different images from each of four categories (total of 96 images varying in valence and arousal) and will be used in Specific Aim 2 with block-randomized amygdala stimulation (see above).

Experimental set-up. The set-up will be similar to one used for the preliminary study (see Fig. 2); the main difference will be the use of a Blackrock CereStim stimulator instead of the Grass 12X used in the pilot, given that the Grass 12X cannot deliver the appropriate stimulation frequency of 100 Hz.

Electrode localization. MRI of the patient will be co-registered with the post-op CT. Amygdala parcellation will be obtained using FreeSurfer sub-field segmentation tool which gives detailed delineation of amygdala sub nuclei (Saygin, 2017).

Electrode types. The human amygdala is approximately 20 mm long on coronal images with the basolateral nuclear group spanning approximately 70% of its length. A standard EEG depth electrode has an inter-electrode spacing of 3 mm and contact length of 2.29 mm. With proper insertion, 5 electrode contacts will span the amygdala, 3 contacts in the BLN, and 2 contacts in the CN (see Fig 5). Some patient may be implanted with depth electrodes which have additional microelectrode contacts. Such microelectrode contacts will not be used in this study.

Location of EBS. We propose that EBS to the BLN of the amygdala for this study for several reasons. First, the BLN is the main site of afferent projections into the amygdala from cortical and subcortical sites (Janak and Tye 2015). Inhibitory EBS in this location will has the highest chance of "blocking" information flow into the amygdala without affecting down-stream networks and thus causing unwanted emotional symptoms. Second, the BLN takes up approximately 70% of the entire volume of the amygdala (~15 mm in length). The PMT 2102-14-091 EEG depth electrode used at DHMC has an inter-electrode spacing of 3 mm and contact length of 2.29 mm, thus resulting in likely 2 to 3 electrode contacts in the BLN in each patient. Therefore, we believe that targeting the BLN for stimulation will be feasible in most patients with amygdala for bipolar EBS. We will target both the right and left amygdala.

Rational choice of EBS parameters. Our intent is to deliver an EBS pulse which will inhibit the BLN. Studies show that EBS in frequencies 100 to 200 Hz inhibit the function of neural structures (Mohan, Watrous et al. 2020). For instance, commercial Medtronic™ DBS systems use frequencies of 130 Hz to inhibit neural networks in Parkinson disease. Furthermore, evidence from studies and our clinical experience with Neuropace™ show that frequencies at 200 Hz are safe to use in patients with epilepsy and inhibit seizures (Sun and Morrell 2014). Lastly, our preliminary study showed that the average afterdischarge threshold in the amygdala is 3.4 mA (about 17μc/cm2) and final safe average stimulation intensity 2.8 mA (12μc/cm2). Based on this evidence from our preliminary study and the literature, our target stimulation parameters will be 200 Hz and intensity of 2.5 mA. These EBS parameters are likely to be safe, not induce afterdischarges, and produce an inhibitory effect on neural structures. If stimulation parameters used in the study result in unexpected effects (such as afterdischarges, seizures, experiential symptoms, or lack of clinical effect on perception of valence), we may determine to change stimulation parameters during the

course of the study. We will adjust stimulation parameters to minimize the side effects and maximize the effectiveness of stimulation. We may for instance lower stimulation intensity or change stimulation frequency. These changes will fall within clinically-determined safety limits: 10-200 Hz (frequency), 0.1- 3 mA (Amplitude/Intensity), and 30-60 microseconds (Pulse duration). If it is determined that a change in stimulation parameters is needed, a request will be formally submitted to the IRB.

Statistical analysis of behavioral data. To account for differences among individuals, we will fit a linear mixed model with random intercepts and slopes to account for individual differences in baseline for valence judgements. In addition to valence, we will analyze the effect of EBS on arousal. In our preliminary study, we found an approximately 20% average change in valence perception in 10 patients. Enrolling 16 patients gives us 90% power in seeing the effect EBS.

EEG pre-processing and analysis. To preprocess EEG data, we will exclude bad channels with artifact, filter line noise, and apply a high-pas filter. We will re-reference to other electrode contacts in the same shaft and subtract this average from each electrode in (local average re-referencing). EEG will be segmented using event triggers. Baseline normalization to -500 ms from each stimulus onset. EEG epochs will be identified using event triggers and each trial will be normalized to a baseline 500 ms prior to stimulus onset. Time-frequency analysis using wavelet transform will be used to obtain an event-related time-frequency spectrogram in each recording location. We will also examine event-related coherence between the BLN of the amygdala, the ventromedial prefrontal cortex, the dorsal anterior cingulate, and anterior insula for both valence and arousal (Korzeniewska, Crainiceanu et al. 2008). Differences in gamma activation and coherence between stimulated and unstimulated trials will be assessed.

The Emotion Self-Rating Scale (ESR) will be used to measure the effect of electrical brain stimulation (EBS) of the amygdala This is a self-reported scale of emotional experience which has also been used in mood-induction work (Schneider et al., 1994). It is similar to other subjective ratings of emotions used in other research. Schneider et al. (1994) used it to assess “valence specificity” for six specific emotions. We will administer this scale to understand if amygdala stimulation induces any subjective experience of emotional states. The scale will be administered electronically (on the testing computer) as the final stimulation parameters are decided for each patient but before we present the Valence/Arousal Task. These changes will fall within clinically-determined safety limits:

10-200 Hz (Frequency), 0.1- 3 mA (Amplitude/Intensity), and 30-60 microseconds (Pulse duration).

7.0 Data and Specimen Banking

Intracranial EEG data will be de-identified and exported using secure methods to the analysis computer located in the Department of Neurology at DHMC. This computer will have standard hospital encryption and password protection. Data from this computer will not be exported to other computers or send over internet channels without appropriate secure protocols. Access to this data will only be made available to the PI and other persons authorized by the study PI. De-identified data will be shared with NIH and/or NIMH data archive for use in future research. No patient identifiers will be included with this data sharing.

Like EEG data, behavioral data and demographics will be de-identified and exported following standard secure protocols to a study computer located at the Department of Neurology. This computer will have standard hospital encryption and password protection. Data from this computer will not be exported to other computers or send over internet channels without appropriate secure protocols. Access to this data will only be made available to the PI and other persons authorized by the study PI. De-identified data will be shared with NIH and/or NIMH data archive for use in future research. No patient identifiers will be included with this data sharing

8.0 Sharing of Results with Subjects

While the results of the daily testing sessions will not be shared with individual participants, we may publish the results of this research.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law.

If there are negative outcomes that led to the termination of the study, these will be published as quickly as possible on the ClinicalTrials.gov website. This website will not include identifiable information.

9.0 Study Timelines

Participants will be enrolled for the duration of their intracranial monitoring admission, approximately 2 – 3 weeks.

- March 31, 2022 – January 1, 2024 – Enrollment of 16 participants, data collection
- January 2, 2024 – January 1, 2025 – Data analysis, reporting, writing manuscripts

Due to COVID-19 pandemic and restrictions on admissions to Dartmouth-Hitchcock of patients with intracranial EEG, the exact timeline for this study is uncertain.

10.0 Inclusion and Exclusion Criteria

Inclusion Criteria:

- Age of 18 years and older
- FSIQ 75 and above or any equivalent test of generalized intelligence as determined by the PI to adequately predict engagement in the task
- Able to give independent consent for participation in the study

Exclusion Criteria:

- Additional neurological disorders (such as dementia, stroke, brain tumor, etc.)
- Any psychiatric condition that would limit their ability to provide consent and/or perform study tasks within normal limits. This would be based on presurgical psychiatric assessment.
- Anything else that, in the opinion of the investigator, might preclude them from participating in the study.

11.0 Vulnerable Populations

As a standard of care, we do not perform implantation of intracranial electrodes in pregnant women. Additionally, we do not plan to enroll prisoners, children, or patients who cannot consent for themselves. We will also be screening for IQ.

However, we do not exclude low-income populations from participation in this research. Subjects will not be compensated for participation in this study and their clinical care decisions will not be influenced by participation, so that will prevent financial incentive or coercion.

12.0 Local Number of Subjects

DHMC Epilepsy Center admits approximately 15 intracranial EEG patients per year. As such, we estimate that we will enroll 16 study subjects over a 2-year period. If we cannot recruit 16 patients during this time, an extension for one year may be required.

13.0 Recruitment Methods

The study will recruit patients who have intracranial EEG electrodes (as described above) for evaluation of candidacy for epilepsy surgery to measure the effect of electrical stimulation of the amygdala on an original psychometric task of perception of affective valence. The patients who are recruited will have epilepsy which has been refractory to all treatment and require brain surgery. All subjects will be 18 years or older, have normal cognition, and will fit all inclusion and exclusion criteria. We will recruit 16 patients over 2 years (ideally 8 males and 8 females). All patients will be recruited for Specific Aim 1, 2A, and 2B. The study will be conducted exclusively on the Epilepsy Monitoring Unit of DHMC. We will recruit patients with electrode in both the right and the left hemispheres. The type of electrodes implanted will be determined by the multidisciplinary team prior to the implant. This could include any FDA approved electrode and will be considered as a part of the standard implant procedure.

Our study team will recruit patients with refractory epilepsy who are undergoing intracranial EEG for evaluation of possible epilepsy surgery. The study will be conducted in patients who *do not* have a diagnosis of aggression or PTSD, i.e. the aim is to use intracranial EEG in patient with epilepsy to understand amygdala physiology and cognitive effect of stimulation. At DHMC, the suitability of each patient with epilepsy for intracranial EEG and the location of implanted electrodes are determined by a multidisciplinary board several months prior to the procedure. As such, by far the most common brain regions implanted for clinical purposes are the amygdala and the hippocampus. Only patients with appropriate electrode locations for clinical purposes and who fulfill the inclusion and exclusion criteria will be enrolled in the study.

All study procedures and tasks will be performed in the EMU and completed during the admission period. We will follow up with the participants a few months after discharge for a simple check in for any complications.

Patients will not receive financial compensation for participation in the research.

14.0 Withdrawal of Subjects

Electrographic seizures are common occurrences during electrical stimulation. Clinical seizures are a rare but expected possible side effect of electrical stimulation.

- If a patient continues to experience electrographic seizures despite maximum precaution with stimulation parameters (e.g. appropriate decrease of stimulation intensity), they will be withdrawn from the study. If changes of stimulation parameters are needed, these changes will fall within clinically-determined safety limits:10-200 Hz (Frequency), 0.1- 3 mA (Amplitude/Intensity), and 30-60 microseconds (Pulse duration).
- If they experience a single clinical seizure, the participant will be approached for testing some time later with new stimulation parameters (lower amplitude of stimulation), if judged to be appropriate. These changes will fall within clinically-determined safety limits: 10-200 Hz (frequency), 0.1- 3 mA (Amplitude/Intensity), and 30-60 microseconds (Pulse duration). The participant (s) will be allowed to continue their participation in the study task on the same day if the PI or another qualified and delegated study staff determines that it is safe for the participant to do so. If a participant reports that the standardized emotional images are excessively disturbing, they will be excluded from participating in the study.

15.0 Risks to Subjects

Although all efforts will be taken to ensure safe stimulation parameters, untoward effects of electrical stimulation are the main potential risk to subjects. Risk of electrical stimulation includes seizures and stimulation-induced symptoms such as nausea or tingling. Patient will be warned about the potential risk of the stimulation prior to being enrolled in the study.

We believe this risk will be minimal. Patients will reside in the Epilepsy Monitoring Unit for entire duration of the study. Electrical stimulation is used frequently in patients with intracranial electrodes for localization of eloquent cortex. As such, clinical and electrographic seizures induced by electrical stimulation for clinical purposes are common. Therefore, standard clinical practices exist to minimize the consequences of such seizures. These clinical practices include the presence of experienced physicians during stimulation, presence of seizure nurses, administration of rescue medication if necessary, etc. Any

seizures induced by stimulation will be handed by the standard protocols which already exist.

- If stimulation produces subjective symptoms, alternate stimulation locations will be looked for.
- If stimulation produces electrographic or clinical seizures, patient will be administered standard seizure treatment and per protocol of the Epilepsy Monitoring Unit.
- If seizures or untoward effects occur, study PI or other physicians trained in epilepsy and seizure disorders will be available immediately to assist.

The second potential risk to subjects is viewing of emotionally provoking images. The OASIS image set is composed of emotional images similar to PG-13 rated movies. Informed consent will be obtained from patients outlining exactly the type of images that patients will be viewing. The study will stop if the patient feels uncomfortable viewing any images. The PI will offer counseling to patients if any images produce negative effects.

There is a slight risk of a breach of confidentiality; however every effort will be made to protect the identities of the participants and the confidentiality of the data. Study data will be kept on secure computers and accessible only to study staff. Published results from the study will not include any identifying information.

All symptoms will be assessed by qualified medical personnel throughout the participant's stay in the EMU. However, for the purposes of this study, we will only record adverse events that occur during the study activities.

16.0 Potential Benefits to Subjects

We do not anticipate that knowledge gained in the study will have immediate benefits to patients who participate. This research may benefit patients with refractory psychiatric disorders.

17.0 Data Management and Confidentiality

The study will have several streams of data. First, demographic data collected on patients. Second, behavioral data collected from the administered task. Third, intracranial EEG data.

Behavioral data and demographics will be de-identified and exported following standard secure protocols to a study computer located at the Department of Neurology. This computer will have standard hospital encryption and password protection. Data from this computer will not be exported to other computers or sent over internet channels without appropriate secure protocols. Access to this data will only be made available to the PI and other persons authorized by the study PI. De-identified data will be shared with NIH and/or NIMH data archive for use in future research. No patient identifiers will be included with this data sharing

Intracranial EEG data will be de-identified and exported using secure methods to the analysis computer located in the Department of Neurology at DHMC. This computer will have standard hospital encryption and password protection. Data from this computer will not be exported to other computers or sent over internet channels without appropriate secure protocols. Access to this data will only be made available to the PI and other persons authorized by the study PI. De-identified data will be shared with NIH and/or NIMH data archive for use in future research. No patient identifiers will be included with this data sharing

The trial will be submitted to the ClinicalTrials.gov according to the specific timelines and will be compliant with the institutional policies. The trial will be published in appropriate clinical journal upon completion.

Records will be retained for 10 years following publication of results from the study.

18.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

The study will be monitored by a physician who is not directly involved in the study, i.e. Independent Safety Monitor (ISM).

- The physician chosen for this role will be a physician in the DHMC Department of Neurology who is not involved in the study and does not has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.)

- The ISM will review the study protocol and confirm how the study will be monitored, including data points and the monitoring schedule.

- After each patient is enrolled, the PI will review the data from stimulation including any electrographic seizures, clinical seizures, and the any psychological impact of the study on the patient. These findings will be presented to the ISM on the schedule outlined below.

- The ISM will monitor after the first two subjects complete the study protocol and then at intervals of every 6 months through study completion.

- Serious Adverse Events will be reported to the IRB within 24 hours of study team awareness. Adverse events will be reported to the IRB annually and the ISM semi-annually.

- Unanticipated problems posing risks to subjects or others will be reported to the Dartmouth IRB using the form: "Unanticipated Problems Posing Risks to Subjects or Others Including Reportable Adverse Events" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Stopping rules

The study will be stopped if it is determined that the stimulation parameters are inducing clinical seizures or undue subjective emotional phenomena. If a seizure occurs with stimulation, the event will be recorded as an adverse event. The IRB will be notified of such adverse events annually and the ISM will be notified semi-annually. Stimulation parameters will be examined and adjusted as needed. If a change in parameters does not mitigate events, the study may be stopped for further evaluation.

Risk mitigation

This study involves two main risks to the patient.

The first risk involves the images presented to the patient during the task. The patient may find images from the OASIS picture set emotionally disturbing.

- To mitigate this risk, patient will be warned and the nature of the images will be described in detail prior to presentation.
- In addition, patient will be told that the images may be disturbing (e.g. "at worst as bad as an R rated movie") and patient will be asked to communicate any discomfort with the investigators.

- Patient will be offered opportunity to stop taking part in the study if this occurs.
- In the very unlikely case that study images produce severe emotional distress, the study PI and the hospital Behavioral Intervention Team (psychologist) will be available to discuss any discomfort.

Second risk of the study involves the danger of induction of clinical seizures during electrical brain stimulation. The PI of this study has participated in stimulation mapping of epilepsy patients since 2006 and has extensive experience in 100's of patients. Stimulation parameters used for this study have been carefully researched and we believe will not produce unexpected effects. The goal of the study is to use stimulation parameters designed to be of minimal risk in induction of seizures or production of any other unpleasant symptoms. Despite these precautions it is still possible that a clinical seizure may occur during the administration of the task. If stimulation parameters induce a clinical seizure:

- The event will be reported as an adverse event, i.e. although seizures are not unexpected, every effort will be made to mitigate them.
- The adverse event will be reported to the IRB annually and to the ISM semi-annually. The stimulation parameters for the event will be reviewed.
- We will determine to best of our knowledge reasonable mitigation steps to prevent a second seizure from occurring.

The entire study is conducted in the EMU, which is an inpatient unit at MHMH and therefore has 24-hour oversight from MD, APRN, and RN, which helps mitigate any risk.

19.0 Provisions to Protect the Privacy Interests of Subjects

All protected health information will be handled in a sensitive manner using standards of the D-HH IRB.

20.0 Compensation for Research-Related Injury

N/A

21.0 Economic Burden to Subjects

Participants will not be charged to participate in this study. Their standard of care billing will not be affected by their participation in this study.

22.0 Consent Process

Informed consent for participation in the study will be obtained prior to any study procedures. Commonly, this occurs at the time of clinic visit several weeks prior to the planned procedure. The consent will fully disclose the nature of the study, the nature of electrical stimulation and the risks associated with it, the nature of the images that will be presented. Consent for the study will be obtained exclusively by the PI. The study will involve patient $\geq$ 18 years of age.

Informed consent for participation in the study will be obtained following the SOP: Informed Consent Process for Research (HRP-090). Only patients who can consent for themselves will be enrolled. Cognitively impaired adults will not be enrolled. Women and minorities are not excluded from the study. The limiting factor in our study is our rural location and demographic outlay. We will recruit as many men as women and as many minorities or underrepresented communities as possible.

23.0 Process to Document Consent in Writing

We will be following SOP: Written Documentation of Consent (HRP-091).

24.0 HIPPA Authorization Waiver

HIPPA Waiver Authorization

- X Waiver of HIPPA Authorization for recruitment
- ☐ Waiver of HIPPA Authorization for study activities

-or-

- ☐ Alteration of HIPPA Authorization; not all required elements or statements are present

1. The research could not practically be conducted without access to and use of PHI, nor without the alteration or waiver because such PHI is needed for recruitment purposes. While eligible participants will be referred to the study by their neurologist/epileptologist, participants' health information is reviewed to determine an appropriate referral and collection of demographic data for the study.

2. As indicated in this protocol, there is a slight risk of a breach of confidentiality; however every effort will be made to protect the identities of the participants and the confidentiality of their PHI, including all data collected throughout the study. Study data will be kept on secure computers and accessible only to authorized personnel. De-identified data will be

shared with NIH and/or NIMH data archive for use in future research. No patient identifiers will be included with this data sharing.

3. All data will be de-identified and kept on a secure computer and exported following standard secure protocols to a study computer located at the Department of Neurology. Only authorized personnel will have access to such data. De-identified data will be shared with NIH and/or NIMH data archive for use in future research. No patient identifiers will be included with this data sharing.

4. The PHI will not be reused or disclosed to any other person or entity, except as required or permitted by law.

25.0 Setting

The study will be conducted in the inpatient EMU at DHMC enrolling patients with refractory epilepsy who are undergoing intracranial EEG for evaluation of possible epilepsy surgery. The study will be conducted in patients who *do not* have a specific psychiatric diagnosis, i.e., the aim is to use intracranial EEG in patients with epilepsy to understand amygdala electrophysiology and cognitive effect of stimulation. At our institution, the suitability of each patient with epilepsy for intracranial EEG and the location of implanted electrodes are determined by a multidisciplinary board several months prior to the procedure. As such, one of the most commonly implanted regions is the amygdala, and frequently also include the anterior insula, the dorsal anterior cingulate, the ventromedial prefrontal lobe, and the hippocampus.

DHMC, a component of D–H, is New Hampshire's only academic medical center in Lebanon; it includes a 396-bed hospital with the only Level 1 trauma center, and the only air ambulance service (DHART). The Lebanon medical center covers more than 2 million square feet. DHMC is composed of Mary Hitchcock Memorial Hospital (MHMH), originally founded in 1893, and The Hitchcock Clinic, which was founded in 1927, and is one of the largest multi-specialty group practices in New England. D–H employs 1,216 physicians, as well as 500 advanced practice registered nurses and physician assistants, working in locations throughout New Hampshire and Vermont. DHMC is the primary teaching hospital for Geisel. It offers 49 accredited residency and fellowship graduate medical education training programs. Approximately 55% of the patients treated at DHMC live in New Hampshire and about 43% live in Vermont.

Department of Neurology has 62 faculty and advanced practice providers placed in nine teams covering all Neurological specialties. Most work is performed from the Lebanon, NH campus but there are also satellite practices in both New Hampshire and Vermont. The Department has recently expanded to include the first Neurology Intensive Care Unit at the medical center. Inpatient units are housed in the MHMH and outpatient offices are housed in the main building as well as the community health practice.

The EMU is located in the hospital and is staffed by the epilepsy team at Dartmouth Hitchcock including residents and fellows. The unit monitors all patients with intracranial EEG and reads all recordings to determine epileptiform activity. This unit is often used for recruitment of study subjects including those with stimulation tasks.

The Dartmouth-Hitchcock Epilepsy Center is the only level 4 epilepsy center in Northern New Hampshire, as recognized by the National Association of Epilepsy Centers (NAEC). Dartmouth-Hitchcock serves a rural population and covers the states of New Hampshire, Vermont and Maine for high-level comprehensive surgical epilepsy care. The center performs about 15 intracranial surgical procedures per year. The center is recognized for surgical care in neocortical epilepsy, responsive brain stimulation and basic and clinic research for cognitive impairment in epilepsy.

The epilepsy center works closely with the Epilepsy Foundation of New England, the Epilepsy Foundation of Vermont as well as other community resource groups such as Outdoor Mindset to reach out to community and promote public education to eliminate the stigma of epilepsy. We address all aspects of epilepsy care and see approximately 1500 unique epilepsy patients per year. All current epilepsy providers will be able to refer patients to the study.

26.0 Resources Available

Equipment
For this study, we will purchase a BlackRock CereStim which has the necessary parameters to conduct this study. The Dartmouth College Research Computing facilities include:

(1) a Dell Blade system consisting of 10-nodes, each of which consists of 2 quad-core 2.6 GHz processors sharing 8G of RAM

(2) 32 dedicated processors sharing 16G of RAM on the campus-wide Discovery multi-processing environment at Dartmouth.

All systems include MPI (message passing interface), parallel MATLAB and have processor-customized installations of LAPACK matrix algebra libraries. All desktops and servers to be used are connected to the DHMC network and are protected by the DHMC firewall. A 600+ node Beowulf cluster is available for shared use.

Environment

The research project leader has been provided research office space necessary for him to administratively oversee the completion of his research study as outlined in this application. He will have ample opportunity to engage the research community as well as collaborators through mentor meetings, research in progress meetings, journal club, and leadership symposium. Access to all the services at DH will provide him tools and resources to complete this project and expand his research knowledge. Collaboration with the Department of Psychology and Brain Sciences on the Dartmouth College campus will provide more opportunity to engage the neurosciences community more broadly and participate in all events.

Computer

All research personnel have assigned Lenovo ThinkPad Notebooks, which allow them to access patient medical records, IRB management systems, and to communicate effectively. All laptops are connected to secure network storage options. Dr. Bujarski uses SuperLab 6 to program the stimulation tasks in his research studies. He also uses the FreeSurfer software program to assist with localizing the electrodes to the amygdala. Dr. Bujarski' s computer is networked to the Natus EEG clinical acquisition system, the Epic electronic medical record, i2B2 cohort building software, RedCap patient database software, and TriNetX software program for deeper dive into patient data searches. Dr. Song uses BrainStorm installed on a signal processing computer. All computers have the Microsoft suite installed which is backed up and updated by information technology personnel in the medical center. High-speed connections will be used to access shared servers and database systems.

Office

An office of around 125 square feet is located at DHMC. The office has space for desk, chairs, tables, and file storage as well as data ports to connect to the computer network and phone lines. Mentors will have office space adjacent to his and will have access to the common space for meeting with mentors and study personnel.

Other
Advanced Imaging Center (AIC) is a research resource created jointly by TSE, GSM, and DHMC in 2006 with infrastructure and equipment support from NIH and Philips that consists of 8,000 square feet of space and is directed by Dr. Paulsen. It houses two MRI suites, surgical prep space for animal procedures, patient exam rooms, small animal imaging systems, and distributed computational resources. Instrumentation includes a dedicated 3T MRI for whole body imaging (Philips Achieva 3.0T X-series), two microCT systems for in vivo small animal imaging and ex vivo specimen scanning (GE Biomedical eXplore Locus and eXplore Locus SP), and a microPET in vivo animal system (Philips MOSAIC). The AIC is physically adjacent to the Center for Surgical Innovation, and together, they create a contiguous space of 20,000 square feet prioritized for translational research that will be available to TPSI trainees. AIC is also home to clinical exam rooms, instrumentation development labs, and houses experimental systems undergoing clinical studies for breast, brain and prostate imaging and image-guidance.

27.0 Multi-Site Research
N/A

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