Study Protocol

Title: Non-Invasive Vagal Nerve Stimulation in Opioid Use Disorders

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PROTOCOL TITLE:
Non-invasive Vagal Nerve Stimulation in Opioid Use Disorders

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REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	12/15/19	New	new
2	1/6/2020	Requested changes from IRB and M. Huber	Yes
3	1/29/20	Response by PI	No
4	9/25/2020	Add MRI, study updates	Yes
5	10/9/2020	Compensation changes – check or ClinCard	Yes
6	11/5/2020	Revised exclusion criteria	Yes
7	11/23/2020	Compensation updates	Yes
8	1/20/2021	Updating psychiatric testing	No
9	3/29/2021	Update assessments, add follow up call	Yes
10	10/14/2021	Revise inc/exc wording	No
11	7/18/2022	Revise eligibility	Yes

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1.0 Study Summary

Study Title	Non-invasive Vagal Nerve Stimulation in Opioid Use Disorders
Study Design	Sham controlled, two groups
Primary Objective	Map physiology of vagal nerve stimulation in patients with OUDs
Secondary Objective(s)	Study #1 maps effect of varying durations of vagal nerve stimulation (nVNS) on craving and sympathetic function; Study #2 explores neurophysiology of nVNS or sham stimulation paired with drug cues.
Research Intervention(s)/ Investigational Agent(s)	Study #1 involves open label dose finding (varying durations of nVNS). Study #2 involves randomization to non-invasive vagal nerve stimulation (nVNS) or sham control stimulation with assessment of brain, behavioral, physiological, and biomarker responses to drug cues and/or craving.
IND/IDE #	IND 52220
Study Population	Men and women with a history of Opioid Use Disorders (OUDs)
Sample Size	N=20 for study 1 and n=20 for study 2
Study Duration for individual participants	2-3 study visits, 6 week follow up call
Study Specific Abbreviations/ Definitions	Non-invasive Vagal nerve stimulation (nVNS or VNS), Opioid Use Disorders (OUDs)

2.0 Objectives*

2.1 The purpose of this study is to measure neural and biomarker correlates of vagal nerve stimulation (VNS) in men and women with a history of Opioid Use Disorders (OUDs). In the UG3 phase we will have two studies, Study #1 will be to optimize dosing (N=20) and Study #2 to measure brain and biological correlates of nVNS versus sham in conjunction with exposure to drug use cues (N=20). We will proceed to the UH3 phase which is a larger study in OUD patients if the goals of the UG3 phase are met per NIDA. Only the UG3 phase is covered here.

2.2 Brain function will be measured with positron emission tomography (PET) and biomarkers will be measured in blood, with an assessment of a broad range of stress responsive sympathetic, hormonal and immune markers

2.3 We hypothesize a decrease in sympathetic function and enhanced anterior cingulate function with VNS.

3.0 Background*

3.1 Opioid Use Disorders (OUDs) are highly prevalent and potentially lethal conditions (21). OUDs are often linked to trauma and posttraumatic stress disorder (PTSD) (2-20) and limited treatment options exist (21-25) the use of nVNS in this project during the opioid withdrawal period represents a new innovation from the current treatments using medication and counseling, widely acknowledged to have limitations for this critical period (26-31). Treatments are needed that address the underlying neurobiology of OUDs involving the sympathetic nervous system, inflammation, and brain areas and systems mediating craving and addiction like dopamine and the anterior cingulate, all potential targets of VNS (32-68, 73-94). VNS is effective for a number of conditions, including depression and epilepsy (69-72) and is effective for the underlying neurobiology of OUDs (96-244). Earlier generations of VNS devices had limited implementation due to the requirement for surgical implantation, cost, inconvenience, and the inability to do placebo comparisons related to ethical considerations (95). The failure of Medicare and therefore other insurance agencies to reimburse for VNS implantation has been a major limitation to date (95). Further innovation lies in the use of HR-PET imaging of the brain with equivalent resolution but lacking technical challenges related to interference of VNS electrical signal with scan acquisition using magnetic pulses seen with fMRI. Use of wearable sensing devices for measurement of sympathetic and parasympathetic function and modelling approaches for verification and

exploration of stimulation parameters represent additional innovations made possible by our collaborations with the Georgia Institute of Technology and the City University of New York. We have a multi-disciplinary and diverse research team of investigators with expertise in engineering, computer sciences, behavior, radiology, modelling, nuclear physics, neuroimmunology, psychiatry, epidemiology, cardiology and biostatistics.

3.2 Our preliminary data on the effects of non-invasive Vagal Nerve Stimulation (nVNS) on stress response in traumatized human subjects and patients with posttraumatic stress disorder (PTSD) show that nVNS reliably blocks peripheral sympathetic and enhances parasympathetic function, reduces inflammatory responses (interleukin-6, or IL-6), and enhances central brain responses (anterior cingulate) to stress (72). We now propose to apply this technology to the treatment of patients with OUDs. Following verification using modelling and determination of optimal dosing parameters, we will use these parameters to assess effects of nVNS versus sham stimulation on opioid craving, peripheral autonomic, cardiovascular, inflammatory, and brain functional responses measured with High-Resolution Positron Emission Tomography (HR-PET) and radiolabeled water to videos of drug cues in recently treated patients with OUDs.

3.3 This project will assess a new device, non-invasive Vagal Nerve Stimulation (nVNS), that does not require surgery or implantation, and that electrically stimulates the vagus nerve as it passes through the neck, dampening the sympathetic nervous system and modulating brain regions in a way that may help patients during the opioid withdrawal period and reduce relapse. Studying the effects of nVNS on opioid craving and brain and physiological responses in patients with OUDs has the potential to reduce relapse and save lives, as well as increase our knowledge of changes to the brain and physiology that underlie OUDs and successful response to treatment.

4.0 Study Endpoints*

4.1 The primary study endpoint is subjective drug craving and change in neurophysiological variables (enhanced anterior cingulate function, increased pre-ejection period (PEP) and photoplethysmogram (PPG) amplitude, both indicating decreased sympathetic function.

5.0 Study Intervention/Investigational Agent

5.1 Description: This study assesses nVNS versus a sham stimulation effects on behaviors of drug craving with and without exposure to

drug cues as well as brain response, neurophysiology and biomarkers. NVNS is applied to the neck and electrically stimulates one of the cranial nerves (the vagus) as it passes through the carotid sheath, exerting effects centrally in the brain and peripherally on autonomic and inflammatory function

5.2 Drug/Device Handling: Active nVNS and sham control are kept by research staff under lock and key and only used for the purposes of the study under supervision of the research coordinator.

5.3 The nVNS device has been approved by the Emory IRB for use in a current study in patients with PTSD. It is non-invasive with minimum side effects and has been shown to be well tolerated and there have been no adverse events or untoward effects in 56 subjects to date.

6.0 Procedures Involved*

6.1 Study Design: Study #1: This is a randomized dose finding study of nVNS versus sham stimulation in patients with a history of Opioid Use Disorders (OUDs). This study will optimize dosing (N=20) by testing different stimulation duration parameters. We will measure how these different parameters affect drug craving using analogue scales (248) as well as physiological signals with wearable sensing devices.

6.2

Study #2 is also in patients with OUDs whose aim is to measure brain and biological correlates of nVNS versus sham in conjunction with exposure to drug use cues (N=20). Active and sham devices are assigned serial numbers by ElectroCore Inc. and delivered to the Data Manager who keeps the blind and assigns to subjects as they are recruited using a random number generator. Subjects then undergo nVNS or sham over one day in conjunction with control neutral versus drug use videos to stimulate craving in conjunction with nVNS or sham with brain imaging, measurement of biomarkers and collection of wearable sensing device data. We proceed to the UH3 phase which is a larger study in OUD patients if the goals of the UG3 phase are met per NIDA. Only the UG3 phase is covered here. We hypothesize a decrease in sympathetic function and interleukin 6 (IL-6, an inflammatory marker) enhanced anterior cingulate function with VNS.

6.3 All subjects undergo assessment with behavioral measures, including the SCID (245, 246), a craving measure called the Clinical Opiate Withdrawal Scale (COWS) (248), the SHAPS-C, NRS pain scale, Addiction Severity Index, The Snaith Hamilton Pleasure Scale-Clinician (251), the Subjective Units of Distress Scale (263) The Visual Analogue Scale (VAS) consists of 10-point lines anchored with "not at all" on one end and

"extremely" on the other where participants report the extent to which they felt any craving for opiates, severity of withdrawal symptoms, and the extent to which the study intervention has helped to ease the cravings.

Medical History, is taken with a structured questionnaire which assess socio-demographic factors, medical history, handedness, history of substance use, medications including antidepressants, mood stabilizer and antipsychotics, usage will be quantitated for number of years of usage for utilization in additional analyses. Urine drug testing may be done at study visits. The Early Trauma Inventory (ETI) is 56-item instrument for measurement of childhood traumatic experiences which has been shown to be reliable and valid. All subjects will be assessed with both the ETI-SF-SR for events before the age of 18 and the Adult Trauma Inventory (ATI) for after age of 18. Reinforcement Learning Task (Positive and Negative Valence Domain): Measures reward attainment using an instrumental conditioning task (90 trials). Trials for this task involve a 3s cue presentation during which subjects choose between two abstract stimuli, followed by an exponentially jittered delay, and then a 3s feedback presentation with positive (monetary win), negative (monetary loss) or neutral outcomes. Reward Motivation Task (Positive Valence Domain): Effort-Expenditure for Rewards Task (EEfRT) is a multi-trial game in which participants are given an opportunity on each trial to choose between two different task difficulty levels in order to obtain monetary rewards.

Study #1: Description of Research Procedures, Monitoring for Safety and Minimization of Risks: Patients with OUDs will undergo stimulation at the different parameters outlined. Subjects will first be outfitted with wearable sensing devices (patches attached to the chest and arms) for measurement of physiological signals including the electrical rhythm of the heart (electroencephalogram) as shown in the figures. These figures outline how parameters of interest like PEP and PPG amplitude are measured. Craving is measured with visual analogue scales. Patients will undergo VNS or sham stimulation while viewing neutral and opioid use related videos.

6.4 Magnetic Resonance Imaging (MRI) of the Brain: Subjects in both Study #1 and Study #2 will undergo MRI brain imaging at CSI for identification of the vagus nerve in the neck. Sequences to be obtained include volumetric interpolated breath-hold examination (VIBE), TR=4.93, TE=2.46, flip angle=9, Field of View 210 mm, 112 slices, voxel .78 x .78 x .8, averages 3, time of acquisition 4:38. 3D constructive interference in steady state (CISS), TR=5.46, TE=2.43, flip angle=42, Field of View 152 mm, 112 slices, voxel .6 x .6 x .6, averages 1, time of acquisition 5:17.

6.5

For Study #2 we look at physiology with nVNS or sham in OUD patients. Brain function will be measured with high resolution positron emission tomography (HR-PET) (264-270), autonomic function with wearable sensing devices, and biomarkers will be measured in blood, with an assessment of a broad range of stress responsive sympathetic, hormonal and immune markers. A complete outline of study procedures for Study #2 is presented in Figure 4.

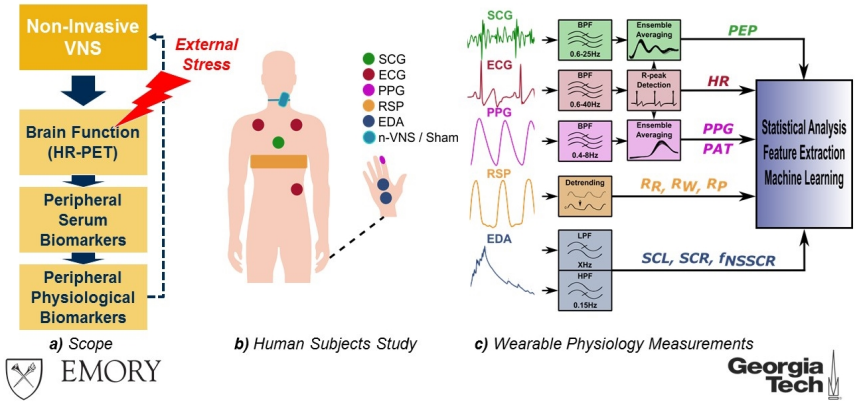

Figure 2: *Measurement of physiological signals using wearable sensing devices in conjunction with nVNS/sham in human subjects. nVNS or sham are attached with a strap to the neck and for electrical stimulation of the vagus nerve as it passes through the carotid sheath. Electrocardiogram (ECG) and seismocardiogram (SCG) are placed on the chest for measurement of heart function and photoplethysmogram (PPG) placed on the finger measures blood volume/peripheral vasoconstriction. The ECG measures the distance on a beat-by-beat basis of the R wave interval (ventricular depolarization, which allows measurement of heart rate (HR) and with SCG pre-ejection period (PEP) as described in Figure 3). Sensing devices on the hand measure electrodermal activity (EDA), with output of skin conductance level (SCL), a marker of sympathetic function. A band on the chest measures respiratory rate (RR), width (RW), and prominence (RP) which tracks parasympathetic function. Data is reduced and analyzed and machine learning models are applied to predict the stimulation type (nVNS or sham). Subjects also undergo brain imaging with High Resolution sPositron Emission Tomography (HR-PET) in Study #2 and magnetic resonance imaging (MRI) of the brain in both studies*

After initial set up and rest period subjects will rest for 30 min. Next, subjects will undergo a series of viewing exercises while lying in the High Resolution Positron Emission Tomography (HR PET) scanner with physiologic monitors attached. After an initial baseline period of resting (condition 1), the subjects will then view two neutral 120 second videos (condition 2), followed by a playback of two opioid use related videos (condition 3). The subject will be instructed to image each event as vividly as possible. VNS or sham will be randomized and given during exposure to the videos. For two of the scans, we are looking at effects of nVNS on the brain with no intervention. The subjects will undergo nVNS vs. Sham VNS stimulation as per published methods (see above).

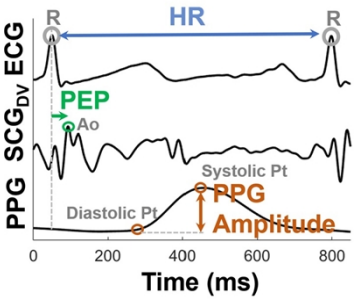

Figure 3. *ECG measures electrical activity of the heart (See Fig. 2) and SCG measures chest wall movements used to register cardiac function including Aortic valve opening (Ao). The time interval between the R wave and Ao is PEP, which shortens with increased cardiac sympathetic tone. The difference in PPG amplitude (see Fig. 2) between time points measures vasoconstriction, an indicator of increased sympathetic function.*

The VAS and SUDS and other behavioral measures are assessed in the beginning and after each task to assess the efficacy of the

trauma recall task in eliciting stress. Patients will stay at the Emory University Center for Systems Imaging while they are undergoing detailed autonomic monitoring and sampling of blood biomarkers. *The blood draws will occur at baseline, 15 minutes before the drug cue task, during the task itself, and then 15, 30, 45, 60, 90, and 120 minutes post-task*.

The "VNS" group will be administered nVNS using the electroCore GammaCore-S non-invasive VNS device. The intensity of the stimulus (i.e. the current amplitude) will be adjusted by the user, to the maximum tolerable level to ensure nVNS without causing excessive pain (typically 10-30 V), the burst frequency to 5 kHz, and the envelope frequency to 25 Hz. These are the standard frequency settings that electroCore has demonstrated to be most effective in capturing the vagus nerve based on evoked potential studies. The duration of delivery will be 2 minutes, and the beginning will coincide with initiation of acquisition of the HR-PET scan which will be 90 seconds in duration; following an additional 8 minutes, a second VNS delivery will be administered, in conjunction with which another scan will be obtained. Each subject in the "SHAM" group will undergo the action of administering the intervention, but the device will be programmed such that the vagus nerve is not actually stimulated.

6.6 Procedures Performed to Lessen Probability or Magnitude of Risks:

- Psychological Assessments: There is a risk that patients may become more upset as a result of being administered questionnaires or assessments. If this occurs they will be assessed by the research coordinator and if needed Dr Bremner or one of the other study psychiatrists on the protocol. If deemed clinically appropriate they will be assessed with the Sheehan Suicidality Scale and if there is a score greater than 0 escorted to the Emergency Room for further evaluation
- Intravenous Catheters and Venipuncture: Placement of an intravenous catheter can result in infection, bruising of the skin, or a blood clot in the vein. The risk of these complications occurring will be reduced by having the procedures performed by a professional under clean conditions and using sterile procedures. Dizziness and fainting are rare risks of blood draws that will be reduced by having the subject supine. There are no long-term side effects.
- Vagal Nerve Stimulation: Stimulation of the vagus nerve may cause muscle twitching, discomfort, or pain during treatment. Hoarseness, a change in voice, or change in taste are other temporary possible consequences but

these resolve when treatment is stopped. These risks will be minimized by stopping the procedure or reducing the intensity of the stimulation

- H2[15O] and PET: H2[15O] or radiolabeled water has been administered to thousands of subjects without side effects or toxicity to date at the doses to be used in this study. Dr Bremner holds an IND for use of radiolabeled water at Emory University. H2[15O] is a radioactive materials. Each patient will have eight H2[15O] blood flow scans. For each O-15 water scan 20 mCi of H2[15O] will be injected as an intravenous bolus. The body organs which receive the highest dose of H2[15O] is the intestine and gonads. The radiation dose to body organs in this study is well within the Food and Drug Administration (FDA) national guidelines for radiation exposure for human research studies and less than the total amount that is permitted for research studies in one year. Risk will be reduced by careful screening. The subjects will be asked if they have participated in research studies that involved radiation over the past year. Risks are reduced by the principles of ALARA, or As Low As Reasonably Allowable, which involves time (reducing time exposure), distance (keeping dose away from subject) and shielding (using lead shields to protect from radiation as much as possible). Risk will also be reduced by ensuring radiation administration is not greater than that outlined in the protocol, and which is below limits for a single session set by regulatory agencies, and that subjects do not participate in more than three research sessions with radiation in a 12 month period, also per guidelines. Also, they will be advised that they should not participate in other research studies involving radioactivity over the next year without consulting Dr. Bremner first. There is a small risk of claustrophobia with PET. If needed the study will be stopped.
- MRI: Subjects can become claustrophobic in the scanner. If needed the study can be stopped or 1-2 mg lorazepam given by mouth. If there is indwelling metal in the head this can cause injury. Subjects will be screened for indwelling metal.
- Opioid Use Related Videos: Viewing videos about opioid use may result in an increase in opioid craving. Viewing videos on smart glasses may cause wooziness or motion sickness. The research staff will debrief subjects, which involves talking about the experiences and helping

subjects to process whatever emotions come up for the subject. If needed, for example if the subject is experiencing suicidal thoughts, further action will be taken if necessary as outlined above. Risks will also be reduced by having the research coordinator talk about their thoughts and feelings and craving after exposure to the drug use video.

- Procedure for Protecting Against Potential Risks: Supervision: All of the scans will be done in the presence of constant supervision with experienced research staff always in attendance and in an institution specifically designed, equipped and functioning in support of these type studies. In the event that some serious medical complications could occur, the PET scan facilities are located in Wesley Woods Hospital on the Emory University campus and can provide immediate care. Confidentiality: All of the information obtained from patients is quoted by number and kept locked in confidential files. This information is available to study investigators. Risk-Benefit Ratio: The risks of participation in this study are small. These are outweighed by the potential benefit which a better understanding of the effects of OUDs could have for society.

- Adverse events (AEs) are evaluated at each visit and reported to IRB using standard Emory IRB reporting guidelines. Serious adverse events (SAEs) (as defined by

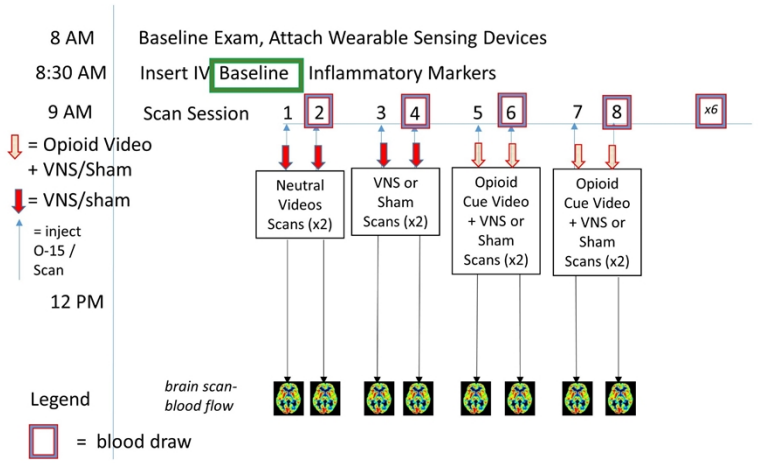

Figure 4*. UG3 Brain Imaging Study Protocol. Patients receive two minute VNS or sham stimulation at onset of opioid cue videos and with no stimulus. Blood is drawn at the time points bounded by purple box. O-15 functional scans show red/yellow activity in cortex.*

CRF 312.32) are reported to the IRB using standard Emory IRB reporting guidelines. All AE and SAE reports will include a description of the event, severity, relationship to the study medication or procedures, any intervention required, and date of the resolution of the event (or otherwise listed as ongoing). SAEs include any fatal event, immediately life threatening event, permanently or significantly disabling event, event requiring prolonged inpatient hospitalization, or any congenital anomaly, and any other event that deems to result in a significant hazard, contraindication, side effect or precaution.

Written IND safety reports will be submitted to the FDA by the IND sponsor, for serious, unexpected suspected adverse reactions within 15 calendar days of learning of its occurrence. If the event is fatal or is deemed to be life threatening, the report will be made within 7 calendar days. The IND sponsor will also make an assessment of whether the event constitutes an unanticipated problem posing risks to subjects or others (UP). This assessment will

be provided to the Emory University IRB, which, in turn will make a final determination. If the Emory IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

- All non-compliance/unanticipated problems, serious adverse events, audits and investigation reports will be reported to the Emory IRB following the standard reporting obligations.
- NVNS devices are provided by ElectroCore Inc, are FDA approved for the treatment of headache, and currently approved by the Emory IRB for the study of PTSD with demonstrated safety and efficacy.
- Included are all surveys and questionnaires. Data stored include information from surveys and questionnaires and all data are stored in the Emory Redcap system.

6.7 Data Collected and Method of Attainment: Data is collected with surveys and questionnaires and stored securely in the Emory Redcap system. Other

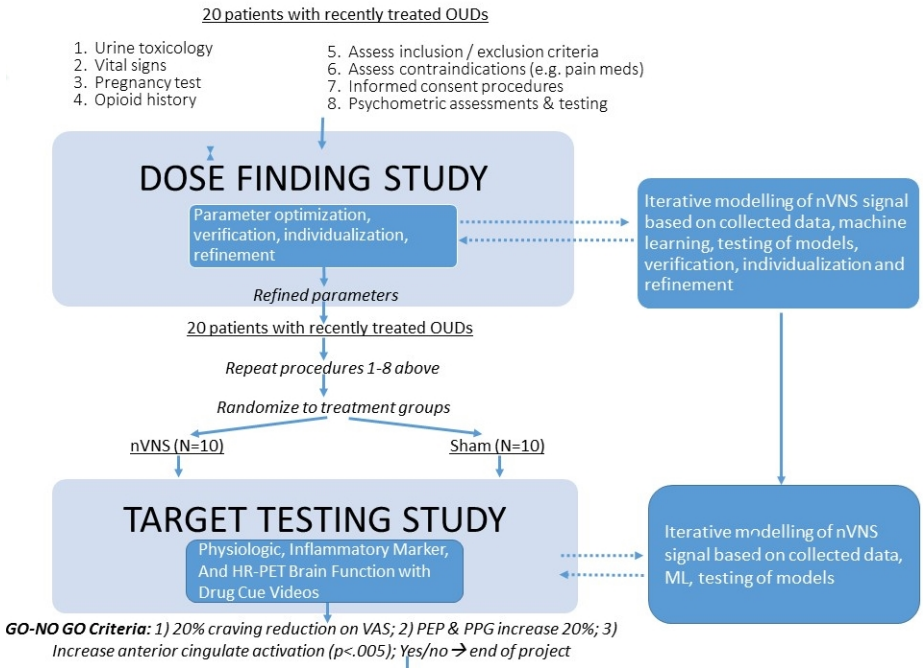

Figure 2*.The UG3 phase involves an initial dose finding and parameter verification phase with iterative modeling and machine learning to refine the protocol in an exploratory open label basis in 20 patients with recently treated OUDs, followed by a second group of similar OUD patients randomized to nVNS or sham with assessment of physiologic, inflammatory, behavioral and brain response to drug cues (videos). Go/No Go criteria determines movement to UH3 phase.*

data collected include blood for measurement of biomarkers, brain imaging data and wearable sensing device (autonomic function) data. Data is kept on secured Emory servers and under double lock and key in EP12 Emory Clinic Psychiatry and the CSI.

7.0 Data and Specimen Banking* N/A ☐

7.1 Data or specimens will not be banked for future use.

7.2 Data will not be stored or associated with each specimen for future use.

7.3 Data or specimens will not be released for future use.

8.0 Sharing of Results with Participants*

8.1 There are no plans to share results with study participants. If we find something of urgent medical importance, then we would like to be able to share it with the participant. This will be a very rare occurrence.

8.2 If the researchers are concerned about something they see on the scan they will tell the participant, and ask them if they want the

scan to be reviewed for healthcare purposes (possibly by other clinicians). They may then be referred for medical treatment. The participant and/or their insurance company may have to pay for the review for healthcare purposes, and for any such treatment.

9.0 Study Timelines*

9.1 Describe:

- The duration of an individual participant's participation in the study will be up to 3 study visits. We may also call them around 6 weeks after the visits to repeat a few questionnaires (Addiction Severity Index, SHAPS-C, COWS, NRS Pain Scale, the Subjective Units of Distress Scale, and the Visual Analogue Scale (VAS)) and see how they are doing. If they took a VNS device home then we will ask them about usage and remind them to return this to the study team.
- We expect to enroll all study participants within 2 years.
- The estimated date for the investigators to complete this study is 3/31/2025 but this depends on whether they are allowed to continue to the UH3 phase. This protocol contains details about the UG3 phase.

10.0 Inclusion and Exclusion Criteria*

10.1 Inclusion and exclusion criteria are listed below. Potential participants will be screened for eligibility by a staff member. We will try to pre-screen subjects via phone using a verbal consent and a waiver of documentation when possible. Otherwise, potential subjects will come in for a screening visit. At the first visit, study staff will confirm eligibility using a checklist.

10.2 The Inclusion and Exclusion Criteria for Study #1: Subjects aged 18 and over who: 1) meet criteria for OUDs based on DSM-5 criteria. The Inclusion and Exclusion Criteria for Study #2: Subjects aged 18 and over who: 1) meet criteria for OUDs based on DSM-5 criteria; 2) have IV access.

Exclusion Criteria: 1) positive pregnancy test; 2) meningitis; 3) moderate traumatic brain injury; 4) neurological disorder or organic mental disorder; 5) history of loss of consciousness greater than one minute; 6) current pregnancy or breastfeeding for women; 7) current or lifetime history of schizophrenia, based on the SCID; 8) a history of serious medical or neurological illness, such as cardiovascular, gastrointestinal, hepatic, renal, neurologic or other systemic illness; 9) evidence of a major medical or neurological illness that is based on the clinical judgment of the study psychiatrist; 10) carotid atherosclerosis; 11) cervical vagotomy.

Several of the above exclusions will be based on the clinical judgment of the study physician. If reviewed and deemed acceptable by the study physician some exclusions may not preclude participation.

10.3 The following populations will also be excluded from the research:

- Adults unable to consent
- Individuals who are not yet adults (infants, children, teenagers)
- Pregnant women
- Prisoners

11.0 Vulnerable Populations* N/A ☒

12.0 Local Number of Participants

12.1 Study #1 will be to optimize dosing (N=20) and Study #2 to measure brain and biological correlates of nVNS versus sham in conjunction with exposure to drug use cues (N=20).

12.2 We will ask IRB to approve 60 enrollees (total) in order to account for some screen failures. We would like to have 20 in each study to complete research procedures.

13.0 Recruitment Methods

13.1 Subjects will be recruited from newspaper advertisements, websites (like Nextdoor) and/or fliers. We may also recruit from the general outpatient population at Emory and the data warehouse. Providers may also refer patients for the study. Participants in previous research studies who have opted in for future contact might also be invited. Once a potential subject is identified, a staff member will schedule a screening interview with them to ensure eligibility with study enrollment criteria. If done via phone, a verbal consent will be obtained by the study staff member. If eligible, subject will sign study consent at first visit before starting any research related procedures. If screening is not able to be done via phone then screening for eligibility will be done in-person.

13.2 Fliers will be used describing the study inclusion criteria and a few of the procedures.

13.3 For study 1:
Compensation ranges from $75 to a total of up to $250 for the study. We will also pay for parking, if needed, at each clinical visit.
Visit 2: $175 ($75 for the MRI and $100 for the visit)
If subjects are given a VNS device to take home, they will get an

additional $75 upon successful return of the device using a prepaid return mailer.

For study 2:
Compensation ranges from $75 to a total of up to $350 for the study. We will also pay for parking, if needed, at each clinical visit.
If used as a backup participant: $50 to cover time and transportation costs
Visit 2: $150 (PET Day)
Visit 3: $75 (MRI Day)
If subjects are given a VNS device to take home, they will get an additional $75 upon successful return of the device using a prepaid return mailer.

Subjects could potentially participate in both studies.

A check will be mailed to the participant after participation is completed. Sometimes this can take 3-4 weeks for Emory to approve and cut the check. Another method of payment that will be offered is using the Greenphire ClinCard system.

14.0 Withdrawal of Participants*

14.1 The PI does not anticipate any circumstances where a participant may wish to withdraw since this study only requires a very short-term in-person participation. However, if after data collection, a participant contacts the PI wishing to not be included in any data analysis/publication, their data will be withdrawn from analysis when possible.

14.2 If the investigator decides to terminate a subject's participation in the research, the investigator will explain to the subject the reasons for this action and, as appropriate, other options for this participant.

14.3 As soon as a participant informs the PI they wish to withdraw, a notation will be made in the subject's binder and/or in Redcap. This documentation will include the date, rationale, and what components of the study for which the subject chooses to continue participation.

15.0 Risks to Participants*

15.1 List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the participants related the participants' participation in the research.

- Psychological questionnaires/interview: Being asked questions about the stress in your life or your mood and opioid use may cause you to have unpleasant and/or upsetting feelings or have an increase in opioid craving. If this happens, then you can take a break from the interviews. You can also slow down and take longer to do the tests. Should you so desire, a counseling session and/or referral for counseling will be made available.
- Physiological monitors: (Biopac, Glove, EDA, PPG, SCG, etc.) These monitors require you to have sensors attached to your skin which may represent an inconvenience to you e.g. when adhesives are removed. They may also cause mild skin irritation or itching. The glove cold application may cause temporary numbness, which stops after application. The hot application may cause temporary redness/skin sensitivity. The subject may feel itchiness due to sensor hookups on hands (due to sticky electrodes and gels) and temporary numbness of the arm is possible, since the subject will remain in the same position for half an hour. The EDA requires you to wear a bracelet-type device during (and possibly after) the visit, which may represent an inconvenience to you.
- Intravenous (IV) catheter and blood draw. The IV can result in infection, bruising of the skin, or a blood clot in the vein. These complications are not common when the catheter is inserted by a professional under clean conditions. Dizziness and fainting are rare risks of blood draws. There are no long-term side effects. The subject may have some discomfort from the blood drawing. The risk from blood drawing is minimal, but may include bruising and infection. The use of sterile precautions will decrease the risk of infection. However, the subject may develop a bruise at the site of the puncture, but this is expected go away in two to three days.
- PET scan: This research study involves exposure to radiation from a Positron Emission tomography (PET) scan. This PET scan procedure is routinely used for medical purposes; however, radioactive water is investigational and not approved by the FDA. This radiation dose is not necessary for a subject's medical care and will occur only as a result of the subject's participation in this study. If a subject has had any significant exposure to radiation over

the past year or plans to participate in other research studies involving radioactivity over the next year, he/she should consult with the study team and Dr. Bremner first. Some people experience anxiety from the PET scan procedure. Viewing videos on smart glasses may cause wooziness or motion sickness. A nurse or technologist will be with the subject during the PET scan procedure. If a subject becomes claustrophobic, anxious or agitated in the PET scanner, the scan will be stopped. If a subject is not able to complete the first PET scan, he/she may not be able to continue in the study. This study will expose subjects to a small amount of radiation. The radiation dose that subjects will receive is equal to or less than the annual radiation exposure limit allowed for persons who are occupationally exposed to radiation (x-ray technicians, radiologist). The principal risk associated with a radiation does is the possibility of developing a radiation-induced cancer later in life. The risk for radiation-induced cancer from this study is minimal. Although the risk from radiation is cumulative it is not expected to adversely affect a subject's condition or treatment. The risk from radiation exposure of this magnitude is considered to be comparable to other everyday risks.

- MRI scan: There is the risk that if subjects have indwelling metallic foreign bodies in the head that MRI scanning may cause local tissue damage. All subjects will be screened for indwelling foreign bodies and individuals with indwelling bodies will be excluded. Some individuals may feel anxiety while in the scanner. If needed, the study will be stopped. There are no other risks of MRI scanning.

  Subjects will be getting a scans (PET/MRI) for research purposes only. The research does not require the scans to be read for healthcare purposes. However, if the researchers are concerned about something they see on the scans they will tell the subject, and ask if he/she wants the scans to be reviewed for healthcare purposes (possibly by other clinicians), and he/she may then be referred for medical treatment.

- Opioid Use Related Videos. The viewing of opioid use related videos may cause some anxiety or feelings of craving for opioids. Subjects are able to stop this test at

any time if they experience anxiety, excessive cravings, or other problems or are uncomfortable with the procedure.

- VNS Testing. Sometimes, a subject may experience hoarseness, shortness of breath, throat pain, cough, abdominal pain, headache, and/or change in voice during treatment. A tingling/pricking/twitching feeling where the device is applied is normal, but should not cause major discomfort. These effects usually stop right away once the treatment is completed. Mild skin irritation or dizziness are other possible side effects. The VNS device should not be used on patients who have any of the following conditions: an active implantable medical device, such as a pacemaker, defibrillator, cochlear implant, and other implanted electronic device; a history of significant carotid atherosclerosis; or a cervical vagotomy.
- Reproductive Risks. Since this research may have bad effects on a fetus and should not be done during pregnancy, it is necessary that a pregnancy test be done first, even if, to the best of the subject's knowledge, they are not pregnant now. Women of childbearing potential will take a urine pregnancy test when they arrive for their visits. If the test is positive they will not be able to participate in the study. This study may be hazardous to a breast-feeding child. Breast feeding mothers may not participate in this study.

  Women who may be pregnant should not be in this study because of possible effects of radiation exposure on their unborn child. Both men who may later father children and women of childbearing potential should be aware that exposure to radiation poses a very slight risk of genetic mutation in the next generation.
- Fasting. In order to undergo study testing, subjects need to be fasting before their study visit for the scan day until the scans are completed. Some people may show discomfort from this prolonged fasting, although true hypoglycemia is rare. A sweetened beverage will be administered if patients complain of lightheadedness or other fasting-related symptoms.

15.2 The long-term effects of the chronic use of VNS have not been evaluated.

15.3 The PET scans and VNS testing may have risks to an embryo or fetus should the subject be or become pregnant.

16.0 Potential Benefits to Participants*

16.1 This study is not designed to directly benefit participants.

17.0 Data Management* and Confidentiality

17.1 We will use analysis of variance models with change in blood flow as dependent variable and absolute blood flow during control task as well as study group as explanatory variables. This analysis will assess differences in brain function according to diagnosis correcting for potential differences in baseline (control task) values. The ANOVA model will be blocked by the matching factor of past alcohol exposure. Analyses will be adjusted for whole brain blood flow. Additional control factors, including patients' age, age of onset of traumatization, years of education, IQ, OUD symptom level and duration of disease, use of oral contraceptive birth control, and smoking, will be entered in the model if they are significantly different between the study groups at an alpha level of 0.25, and/or if they are found to be confounders in the analysis, i.e., if they cause a change of >10% in the parameter estimate for study group when entered in the model. Adjusted means of blood flow will be computed for each combination of group and task to better describe the results. Point estimates and confidence intervals for the difference between groups will be assessed before and after including the covariables mentioned above in the model. Additional analyses will compare OUD patients with and without a history of co-morbid depression.

In all these analyses linear model assumptions, adequacy of fit, and presence of outliers will be checked by inspecting residual plots and influence statistics. Collinearity for variables included in the model will also be checked. Appropriate remedies will be applied, if necessary, to improve model fit and minimize collinearity.

Additional exploratory analyses will use subtraction analysis techniques to look for additional areas of activation for the purpose of generating hypotheses for future studies. Images of absolute blood flow will be subjected to a subtraction type analysis. Images will be realigned to the first image in the series and warped into a common anatomical space using methods described in the preliminary results. Images will be then analyzed using the general linear model of Friston for statistical analysis. The mean of blood flow scans within condition will be calculated and comparisons performed between conditions to assess blood flow with the condition. Areas of increased and decreased blood flow within patient group will be examined, as well as the interaction between

condition and diagnostic group. Images of t statistic will be created and surveyed for hypothesized regions (i.e. medial prefrontal cortex) where uncorrected z score values are greater than 2.86 (corresponding to a corrected p value of > 0.005).

Calculation of Sample Size

For calculation of sample size needed for PET measurement of anterior cingulate activation, we used values for blood flow in the amygdala (scaled to whole brain blood flow) based on previous pilot data. Fear-related tasks resulted in a 6.9 + 4.8% increase in amygdala blood flow versus 1.2 + 1.4% in controls (effect size 1.39). With two tails, an alpha value set at 0.05 and a power of 0.80, 10 subjects are needed in each group (VNS v sham) to show a significant difference between patients and controls (i.e. group by condition interaction). The number of subjects in each group will therefore be adequate to answer the questions proposed in this study.

17.2 All study staff will take required training prior to working with participants and/or PHI. All data will be kept in either locked offices in secure buildings or online via Redcap or on a password restricted research server. A certificate of confidentiality will be in place. Confidentiality will be assured by the use of subject codes when possible rather than personal identifiers. After the study is completed, the study database will be secured, and information will only be entered using subject identifier codes rather than personal identifiers. Published results will be presented as group data, without identifiers.

17.3 A (bi) weekly meeting with the staff, Study Coordinator and the PI is held to discuss any issues that may arise. A review of data is done for accuracy and protocol compliance. Data collection forms are verified for accuracy before storing in database. Describe any procedures that will be used for quality control of collected data.

17.4 Describe how data or specimens will be handled study-wide:

- Study ID, date of visit, and type of sample will be included for each specimen
- Specimens will be stored in a -80 freezer at EP12 or RSPH
- Specimens will be stored until they are fully utilized for testing
- The Pearce Lab and the study team will have access to the data and/or specimens
- The Pearce Lab uses a spreadsheet system to inventory what has been brought to their lab for testing. A study team member will deliver the samples and the lab will sign off on

the delivery. The data will be sent from Dr. Pearce to the PI and/or study staff for saving to the research server.

- Specimens will be transported via dry ice using coolers from Wesley Woods and/or EP12 to the Pearce Lab in RSPH.

18.0 Provisions to Monitor the Data to Ensure the Safety of Participants*

18.1 Describe:

- The Data Safety Monitoring Plan (DSMP) outlined below will adhere to the protocol approved by the institutional IRB responsible for study oversight. An IRB-approved written informed consent will be obtained from each subject at entry into the study; elements of informed consent will include: (a) having the subject review the study consent form; (b) having the investigator(s) or study staff meet with the subject to review the consent, confirm understanding, and answer any questions; and (c) once the investigator(s) or study staff are convinced that the protocol is understood and that there is agreement to participate, having the consent signed. A copy of the signed consent form will be provided to subject. Documentation of the informed consent process will be made in the research and/or medical records as appropriate or in Redcap. The principal investigator (PI) or his designated appointee will review data collection forms for completeness and accuracy of the data as well as protocol compliance on an as needed basis. Any data inconsistencies will be resolved by study staff as soon as possible. The PI will review this protocol on a continuing basis for subject safety and protocol deviations or study noncompliance. Reportable Events will be communicated to the local institutional IRB as required. Self-monitoring will be completed by the study staff every 6 months. All findings/observations related to safety will be documented in REDCap and shared with the study team as well as independent monitor. Any candidate safety-related adverse events will be discussed immediately, and the independent monitor will provide recommendations about the next best steps.

  Stopping Rules for Mental Stress Testing.
  Absolute Indications for Termination
  - Moderate-to-severe chest pain at a level that the patient wishes to stop.
  - Central nervous system symptoms (eg, ataxia, dizziness, or near syncope).
  - Signs of poor perfusion (cyanosis or pallor).
  - If the patient becomes excessively anxious or uncomfortable, or requests us to stop.

  Relative Indications for Termination

- Drop in systolic blood pressure >10 mm Hg (persistently below baseline) despite an increase in workload, in the absence of other evidence of ischemia.
- Increasing chest pain.
- Fatigue, shortness of breath, or wheezing
- General appearance (see below).
- Hypertensive response (systolic blood pressure >250 mm Hg)
- Development of bundle-branch block that cannot be distinguished from ventricular tachycardia.

Stopping Rules for Study

Absolute indications for study wide termination (determined by the PI)

- the intervention is associated with adverse effects that call into question the safety of the intervention
- difficulty in study recruitment or retention that will significantly impact the ability to evaluate the study endpoints
- any new information becomes available during the trial that necessitates stopping the trial
- other situations occur that might warrant stopping the trial

Plans for transmission of temporary or permanent suspension actions: Any actions that mandate temporary or permanent suspension of study will be transmitted to the institutional IRB, and, if appropriate, to the IND sponsor, FDA, or the National Institutes of Health.

Plans for protecting subject confidentiality: All information and materials that are obtained for research purposes only will be kept in strict confidence. Confidentiality will be assured by the use of subject codes when possible rather than personal identifiers. After the study is completed, the study database will be secured, and information will only be entered using subject identifier codes rather than personal identifiers.

Plans for assuring data accuracy and protocol human safety compliance: An IRB-approved written informed consent will be obtained from each subject at entry into the study; elements of informed consent will include: (a) having the subject review the study consent form; (b) having the investigator(s) or study staff meet with the subject to review the consent, confirm understanding, and answer any questions; and (c) once the investigator(s) or study staff are convinced that the protocol is understood and that there is agreement to participate, having the consent signed. A (bi) weekly meeting with the staff, Study Coordinator and the PI is held to discuss any issues that may arise. A review of data is done for accuracy and protocol compliance. Data collection forms are verified for

accuracy before storing in database. The PI will review this protocol on a continuing basis for subject safety. Patient Monitoring: will be performed by the PI, the Co-Investigators, and the Research Coordinator(s). Any unanticipated events are reported to the IRB in a timely manner per protocol.

The above detailed plans should assure data accuracy and protocol human safety compliance for this study. These include computerized database management, and IRB oversight and communication. This plan, together with oversight by the IRB, should be sufficient for studies that do not require a DSMB.
The Independent Monitor for this study is Dr. Jeanie Park. Dr. Park is not associated with this research project and thus works independently of the PI, Dr. Bremner. Dr. Park is not a part of the key personnel involved in this grant, and is qualified to review the patient safety data generated by this study because of her unique expertise in autonomic physiology. Dr. Park's CV is attached.
She will review documentation of subject-reported adverse events every 6 months.

19.0 Provisions to Protect the Privacy Interests of Participants

19.1 Participants will be interviewed in private research room with the study staff. A Certificate of Confidentiality is in place since this is funded by NIH/NIDA. Sensitive questions will only be asked as needed for scientific aims.

19.2 Study staff will strive to limit interactions from people outside of the study team. Private areas will be used when possible. The study staff will explain study procedures to the participant. At any time, the participant is able to request a break or skip a question if s/he is uncomfortable with the question and/or interview.

19.3 The study team is able to access any information at any time since they are protecting all the hardcopy and digital data. No one else outside of the study team will be able to access the information.

20.0 Economic Burden to Participants

20.1 Participants will not have any costs, except for basic things like transportation, for participating in the research.

21.0 Consent Process

21.1 Verbal consent may be done for screening purposes to ensure the subject is eligible for the study. If not, screening will be done at the first in-person visit.

At the first clinic visit, the study staff will begin the visit with the signing of the informed consent. After signing the consent form, they will begin the study procedures.

- The consent process will take place at either Wesley Woods, EP12, Emory Clinics, or RSPH.
- The study will be discussed with the potential participant prior to the visit. The study will begin after the consent process.
- The study staff will ensure that the participant continues to understand the procedures and will answer any questions that come up.
- Informed Consent Process:
    - One of the study coordinators will lead the informed consent process.
    - The consent discussion will vary but should take around 15-20 minutes prior to any procedures being done.
    - Once at the research center, the research coordinator will discuss all aspects of the research protocol with the subject and go over the consent and any questions they may have in regards to the study. After the discussion, the research coordinator will ask the subject if they wish to participate in this study and both will sign the written consent. The subject will be given a copy of the consent to keep. The consent clearly states that participation in this study is voluntary and they can leave the study at any time, for any reason or for no reason. If they withdraw they will still keep all health care services that they would expect from Emory University and their affiliates.
    - Subjects will be asked to restate some of what they have heard in order to make sure they are aware of all procedures.

Non-English Speaking Participants *N/A* ☒

Participants who are not yet adults (infants, children, teenagers) *N/A* ☒

Cognitively Impaired Adults *N/A* ☒

Adults Unable to Consent *N/A* ☒

22.0 Process to Document Consent in Writing

22.1 Consent of the subject will be documented in writing in the subject's chart or in Redcap.

23.0 Setting

23.1 Describe the sites or locations where your research team will conduct the research.

- Subjects will be recruited from the clinic, newspaper advertisements, online websites, referrals, and/or fliers.
- Research procedures will be performed at Emory Clinics, Wesley Woods, and/or Executive Park 12 research rooms.
- Local detox or drug treatment centers might be used as sites with an IRB approved Site permission letter.

24.0 Resources Available

24.1 Describe the resources available to conduct the research:

- Subjects in this study will be patients with opioid use disorders based on DSM-5 criteria recruited from the greater Atlanta metropolitan area. We will study patients with OUDs on medication treatment. According to the Substance Abuse and Mental Health Services Administration (SAMHSA), 109,777 (4.18%) have non-medical use of prescription pain relievers, and 48,302 are estimated to have an OUD. Based on this, there is an ample population of individuals for the study.
- Recruitments for studies 1 and 2 will take place over two years.
- Emory is one of the top biomedical research institutions in the nation, ranking among the top 20 schools of medicine in NIH research funding, at $218 million in 2008. Emory has more than 2,500 faculty members. Emory Healthcare, which includes Emory's own or affiliated clinics and hospitals, is the largest service provider in Georgia. The clinics and hospitals, with almost 3,000 inpatient beds and more than 2 million annual outpatient and emergency visits, create an exceptional environment for patient-oriented research. Emory physicians also provide a major portion of the city's indigent and public health care. It is considered to be the premier institution for cardiology and cardiac surgery care in the Southeastern United States. Atlanta has also one of the largest African American populations of any city in the U.S. and approximately 30% of all patients in Emory Healthcare hospitals and clinics are African American in origin.
- **Emory Brain Health Center and Department of Psychiatry.** The Emory Department of Psychiatry & Behavioral Sciences, chaired by Mark Rapaport, M.D., is one of the most exciting and rapidly growing psychiatry departments in the U.S. today. The faculty of the department actively pursue goals of innovation in research, education and delivery of care. Emory has moved from being a primarily a clinical and regional department to one of the most rapidly expanding psychiatry departments in the country. Drs. Rapaport, Bremner, Welsh

and Dudley are all clinical psychiatrists in the Emory Clinic Psychiatry located at the Emory Brain Health Center in Executive Park, Atlanta, Georgia. Drs Welsh and Dudley have access to hundreds of patients with opioid use disorders. The department now has a number of NIMH-funded investigators, and the Psychiatry Department within **Woodruff Memorial Building** (WMB) has basic research laboratories for psychiatry faculty. The laboratories include facilities for molecular biology, neurochemistry, in vitro autoradiography, and psychopharmacology. One of the highlights of working at Emory is the lack of boundaries between departments, the warm collegiality, and the opportunity to collaborate with other scientists in different departments, as well as at Emory College, the CDC, and Georgia Tech. A number of our faculty have joint appointments and laboratory space as well as active collaborations with the **Center for Disease Control (CDC).** The CDC is conveniently located on the Emory Campus. Highlights of the program include collaborations in Chronic Fatigue Syndrome, Psychoimmunology, and Mind-Body interactions. The **Wesley Woods Hospital** has large inpatient and outpatient programs in geriatric psychiatry with active research programs. **Emory Clinic** is our outpatient adult psychiatry clinic and is an excellent source for research subject recruitment. At **Grady Hospital,** the public hospital which serves Fulton and DeKalb counties, there are both inpatient and outpatient psychiatric treatment facilities, laboratory space, and active research programs. The Emory faculty treat the Grady patient population through a foundation program. Many of our faculty are located at the **Yerkes Regional Primate Center** and the **Center for Behavioral Neuroscience,** which are described in more detail below. Other programs in which Psychiatry faculty collaborate or participate are listed below.

- The Department of Psychiatry is part of the **Emory Brain Health Center**, located at the newly-built Executive Park site of Emory Healthcare. As a part of the Emory Healthcare Network, the Center brings together more than 400 researchers and clinicians specializing in neurology, psychiatry and behavioral sciences, neurosurgery, rehabilitation medicine, and sleep medicine to more rapidly predict, prevent, treat, and cure devastating diseases and disorders of the brain. The Emory Brain Health Center holds more than 20 centers and programs including the Child and Adolescent Mood Program, Epilepsy Center, Pituitary

Center, Stroke Center, Treatment Resistant Depression Program, and Veterans Program. The facility has fully equipped conference rooms, office rooms, and rooms dedicated to research subject interview purposes. The **Child and Adolescent Mood Program (CAMP)** is located on the second floor of the Emory Brain Health Center. CAMP offers services including psychopharmacological evaluations, medication management, individual therapy, and various psychological testing to children and adolescents. As part of CAMP, **Emory Adolescent Substance Use Treatment Services (EAST)**, Directed by Justine Welsh, M.D., a co-investigator on this project, provides psychiatric and behavioral interventions to adolescents and young adults with substance use disorders. The clinic is equipped with a clinical laboratory and ancillary services. The clinical laboratory is capable of running various urine analyses and blood sample tests. A full-time LCSW certified to provide Adolescent Community Reinforcement Approach (A-CRA) therapy is available to provide treatment on site. Fidelity for A-CRA will be measured by recorded session procedures. Recording devices are on site and available to each provider. Limited counseling sessions will also be documented to monitor endorsed medication adherence, medication side effects, assessment of withdrawal/cravings and reasons for any dose adjustment in the electronic health record. The Department of Psychiatry and Behavioral Sciences will provide administrative and computer support.

- **Emory Clinical Neuroscience Research Unit (ECNRU)**. The ECNRU, J. Douglas Bremner, MD, Director, is a research program at the Emory Briarcliff campus for the study of the neurobiology of PTSD and depression and mechanisms of these disorders in heart disease. There is 5,000 square feet of space including offices and cubicles for the PI and staff and an image processing laboratory.
- **Pearce Lab**: A number of serum biomarker analysis instrumentation tools are available to Dr. Brad Pearce in his molecular neuroimmunology laboratory space. In addition, the RSPH supplies a shared equipment facility for Dr. Pearce and other PIs on the 4th floor. This facility includes a BioRad Chemidoc XRSt gel imaging system, an Applied Biosystems 7500 Fast Real-Time PCR System, Biotek Epoch plate reader with 200 nm to 999 nm wavelength range and 6- to 384- microplate reading capability, and BLX405 plate washer, Sorvall RC64 centrifuge, Eppendorf 5810R bench-top centrifuge, a Perkin Elmer Victor3 1420 fluorescence and luminescence multilabel

plate reader, and a Beckman Optima L Series Ultracentrifuge. In addition, Dr. Pearce routinely uses the Emory University Flow Cytometry Core Facility for his immunology work. This facility includes the BD FACSort two-laser, four-color benchtop analyzer. In addition, the Emory Multiplexed Immunoassay Core provides Dr. Pearce and other Emory researchers with use of equipment (SECTOR Imager 2400), training and expertise for the Meso Scale Discovery Platform. This immunoassay platform uses electrochemiluminescence (ECL) detection based on ruthenium(II)-tris-bipyridine derivatives. The sensitivity and dynamic range of the platform is better than most ELISAs and has shown fewer matrix effects than ctytobead systems. We routinely use this multiplex assay platform for other studies.

- **Emory Center for Systems Imaging (CSI).** The neuroimaging facilities at Emory include three research dedicated, Siemens 3T Prisma and Trio scanners. All of the functional magnetic resonance imaging (fMRI) facilities are equipped with conventional 12-channel head coils, 32-channel head coils, and new 64-channel head coils that allow for state of the art, high temporal and spatial resolution, functional MRI. In particular,
these systems are equipped with 32 channels, which can be configured in a wide variety of combinations through the TIM software. It includes standard sequences for EPI BOLD, diffusion, perfusion imaging, and Diffusion Tensor Imaging (DTI). We will have a variety of coils, including a 32-channel head coil, 12-channel head coil, transmit/receive birdcage head coil, flex coils, neck matrix and spine matrix coils. The neuroimaging community at Emory is comprised of the Biomedical Information Technology Center (BITC), Center for Systems Imaging (CSI), and the Facility for Education and Research in Neuroscience (FERN). Each of these centers are fully staffed with expert MRI physicists, MRI technicians, and cognitive neuroscientists. All of these
centers feature (a) MRI simulator ("mock scanner"), to acclimate participants to the imaging environment and train them to remain still (critically important for pediatric and special populations); (b) full psychophysiology recording suite (Biopac: heart rate, startle, skin conductance); (c) Eye-Link MRI compatible eye tracker; (d) behavioral testing space; and (e) computer room, for data processing and analysis. The major imaging equipment housed at CSI includes a cyclotron/Radiochemistry lab, a 3T MRI system, a High Resolution Research Tomograph (HRRT, CTI Corp.) human brain High Resolution Positron Emission Tomography (HRPET) system, an Inveon micro Positron Emission Tomography-Computed Tomography (PET-CT) system, and a multispectral fluorescence animal imaging system. The Wesley Woods

Medical Center has a brain dedicated High Resolution Research Tomograph (HRRT) obtained with a National Center for Research Resources (NCRR) and Georgia Research Alliance (GRA) grant to Dr. Doug Bremner. Other facilities include an on site cyclotron and radiochemistry facilities including hot cells and robotic arms as well as a high resolution 3T MRI.

- **The Center for Systems Imaging (CSI) Radiochemistry Lab** This resource is directed by Dr. Mark Goodman and is located on the 2nd floor of the Wesley Woods Health Center. It houses a Siemens RDS 111 multiport, self-shielded, automated cyclotron producing a 11 MeV, 50 µA proton beam. The cyclotron is equipped with targets for the routine production of curie amounts of [18F]fluoride, [18F]fluorine, [11C]carbon dioxide, and [15O]oxygen. The radiochemistry area is a 2,100 square foot cyclotron vault and laboratory which includes:
    - four master slave manipulator arm-equipped hot cells
    - five mini-cells
    - one Siemens computer programmable two reaction vessel radiochemical processing unit
    - one GE TracerLab FXN unit
    - one semi-automated remote mini-syringe pump
    - two reaction vessel radiochemical processing units
    - one semi-automated remote mini-syringe pump fluorine-18 F2 radiochemical processing unit
    - one automated oxygen-15 water synthesis module
    - one GE PETtrace carbon-11 methyl iodide module
    - one clean room , hot and cold waste systems and ventilation chemical and radiation monitoring systems.

  The radiochemistry laboratory is equipped with four pneumatic tube systems located in the four hot cells for rapid delivery of radiopharmaceuticals. It also has a variety of modern analytical instruments which include
    - one Carroll and Ramsey Associates eleven probe radiation detection system
    - one Waters Alliance radio-HPLC unit that is configured with UV/Vis and IN/US Radiometric detectors and one Waters radio-HPLC unit that is configured with UV/Vis and Bioscan Radiometric detectors
    - one Raytest radioactivity thin-layer chromatography system
    - two electrically activated rheodyne HPLC injectors
    - eight manual rheodyne HPLC injectors and 4 Waters' 515 HPLC pumps
    - one Bioscan hot cell radiometric detector

• one Agilent 6890N radio-gas chromatograph equipped with a thermal conductivity and flame ionization detectors
• one Oxford sodium iodide detector and well counter/multichannel analyzer
• two Capintec 712M dose calibrators with four remote ionization chambers and four remote readouts and four Mettler electronic balances.

Here is a list of tracers currently produced:

2-FDG (PETNET) Human
C-11 HOMADAM (WW-CSI & Yerkes#) Human
N-13 NH3 (PETNET) Human
F-18 FECNT (WW-CSI & Yerkes#) Human
C-11 PIB (WW-CSI & Yerkes#) Human
F-18 FACBC (WW-CSI & Yerkes#) Human
C-11 Flumanezil (WW-CSI & Yerkes#) Human
F-18 FACPC (WW-CSI & Yerkes#) Human
C-11 Raclopride (WW-CSI & Yerkes#) Human
F-18 FEmZIENT* (WW-CSI & Yerkes#) Animal
O-15 Water (WW-CSI) Human
F-18 FEpZIENT* (WW-CSI & Yerkes#) Animal
O-15 Oxygen (WW-CSI) Human
C-11 MENET* (WW-CSI & Yerkes#) Animal
F-18 Fallypride (WW-CSI & Yerkes#) Animal
Cu-64 ligands (WW-CSI & Yerkes#) Animal
F-18 WAY (WW-CSI & Yerkes#) Animal
C-11 MDL (WW-CSI & Yerkes#) Animal
C-11 WAY (WW-CSI & Yerkes#) Animal
F-18 FMISO (WW-CSI & Yerkes#) Animal
*eIND in progress for first in humans
#Yerkes only animals

- **Georgia Tech/Emory Department of Biomedical Engineering** In September 1997, after an intense planning and review process that involved faculty from both institutions, Georgia Tech joined with Emory University School of Medicine to establish the Georgia Tech/Emory Department of Biomedical Engineering (BME) (Michael Thomas, PhD, Acting Chairman). This new academic unit is a unique partnership between a public and a private institution. Dr. Clifford is a faculty member in this department. This Department represents the strong commitment that both Emory and Georgia Tech have toward enhancing research in the biomedical and bioengineering sciences, and will significantly enhance research and education opportunities in these areas. State-of-the-art facilities are available at Georgia Tech, including the new biocomplex building to be completed in the future. Georgia Tech

is located just west of downtown Atlanta, about 15 minutes from the Emory campus.

- **The Inan Research Group** is housed in the Technology Square Research Building (TSRB), one of eleven buildings on the campus that houses Electrical and Computer Engineering (ECE) faculty. The Inan Research Group has its own lab space in TSRB, with state-of-the-art test instruments including oscilloscopes, function generators, power supplies, multimeters, and signal analyzers. The lab is also well-equipped for rapid electromechanical prototyping (e.g., soldering stations, hand tools), physiological monitoring, and data acquisition, and includes computers, microcontroller and sensor evaluation boards, and all other necessary tools for prototyping and evaluating the proposed hardware. For data analysis and visualization, in addition to the computers in the lab, there is a separate student carrel space with computers equipped with necessary specialized software tools (e.g., MATLAB, SolidWorks).
- **Neural Engineering Group, City University of New York**
  The Neural Engineering Group at The City College of New York, directed by Marom Bikson, Ph.D., analyzes nervous system function at multiple scales spanning sub-cellular, single cell, tissue, animal, to human cognitive levels. Similarly, our translational research and development program integrates experimental testing, medical device development, and clinical trials – with the over-arching goal of improving human health through engineering innovation.

- There is a risk that patients may become more upset as a result of being administered questionnaires or assessments. If this occurs they will be assessed by the research coordinator and if needed Dr. Bremner or one of the other study psychiatrists on the protocol (Drs. Welsh, Dudley).
- Viewing videos about opioid use may result in an increase in opioid craving. The research staff will debrief subjects, which involves talking about the experiences and helping subjects to process whatever emotions come up for the subject. If needed, for example if the subject is experiencing suicidal thoughts, further action will be taken if necessary. For example, if subjects are suicidal they will be escorted to the Emergency Room, and they will be instructed that if they have problems with feeling upset they should call one of the clinicians and if they develop active suicidal ideation with a plan they should go to the Emergency Room.
- A (bi) weekly meeting with the staff, Study Coordinator and the PI will be held to discuss any issues that may arise and to ensure that all persons assisting with the research are adequately informed

about the protocol, the research procedures, and their duties and functions.

25.0 Multi-Site Research when Emory is the Lead Site*N/A ☒

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