MGB HealthCare System
Research Consent Form

Subject Name:
MRN or DOB:
Subject Identification

Certificate of Confidentiality Template
Version Date: January 2018

Protocol Title: Brain Mechanisms of vagus nerve stimulation and stress reduction training for migraine

Principal Investigator: Vitaly Napadow PhD

Site Principal Investigator:

Description of Subject Population: Migraine Patients

About this consent form

Please read this form carefully. It tells you important information about a research study. A member of our research team will also talk to you about taking part in this research study. People who agree to take part in research studies are called "subjects." This term will be used throughout this consent form.

MGB HealthCare System is made up of MGB hospitals, health care providers, and researchers. .

If you have any questions about the research or about this form, please ask us. Taking part in this research study is up to you. If you decide to take part in this research study, you must sign this form to show that you want to take part. We will give you a signed copy of this form to keep.

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov,* as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Why is this research study being done?

In this research study we want to learn more about migraines.

Dr. Napadow, the Principal Investigator on this study, is an inventor of technology that is used in this study. The hospital owns this technology and therefore Dr. Napadow and the hospital may benefit financially if this study shows that the technology is valuable. The hospital's conflict of interest policies are handled by the hospital's owner, MGB HealthCare. In accordance with these policies, MGB has determined that the interests create no significant risk to the welfare of participants in this study or to the integrity of the research. If you want more information about this, please contact the MGB Office for Interactions with Industry at 857-282-2024.

How long will I take part in this research study?

As a part of this study, we will ask you to come to the Charlestown Navy Yard campus of MGH and to CHA for 23 total in-person/online visits: 4 visits at MGH prior to treatment, 16 treatment visits at CHA, and 3 visits at MGH after treatment. The in-person/online treatment visits will occur twice per week for 8 weeks. Additionally, we will ask you to participate in 8 online treatment visits. The online treatment visits will occur once per week. We will ask you to complete daily diaries of your migraine symptoms for the duration of the study. These diaries are electronic and will be available to you each day using a web-browser from either your phone or a computer.

You will also be asked to engage in a home activity 4 out of 7 days of the week during the 8-week treatment visits.

It will take about 42 weeks to complete the study.

There will also be a 3- and 6-month follow-up visit which will include the completion of online questionnaires. These visits do not require a visit to MGH or CHA and can be completed at home.

What will happen in this research study?

If you decide to join this research study, the following things will happen including personal health tracking, surveys, blood draws, an injection and IV placement, MRI scans, PET scans, and office visits.

Why might you choose to take part in this study?

We cannot promise any benefits to you from taking part in this research study. Others with migraines may benefit in the future from what we learn in this study.

Why might you choose NOT to take part in this study?

Taking part in this research study has some risks and requirements that you should consider carefully. A detailed description of all side effects, risks, and possible discomforts can be found later in this consent form in the section called “What are the risks and possible discomforts from being in this research study?” Other things to consider are the time commitment and travel requirements to the Charlestown Navy Yard and the Cambridge Health Alliance.

What other treatments or procedures are available for my condition?

You do not have to take part in this study to be treated for migraine. Mindfulness meditation, progressive muscle relaxation, and psychoeducation are available outside of this research study. Other treatments are available for migraine including medications and other treatments that do not include drugs. The study staff will discuss with you the benefits and risks of other treatments

Detailed Information

Why is this research study being done?

The purpose of this study is to explore how a stress reduction program to help manage migraine, in conjunction with brief stimulation of the vagus nerve using a procedure called tVNS, affect the brains of migraine patients. This study uses two types of brain imaging to understand these effects. Functional MRI (fMRI) scan can take detailed pictures of the brain and a Positron Emission Tomography (PET) scan allows us to see areas of the brain exhibiting inflammation. The fMRI allows investigators to evaluate changes in how blood flows to parts of your brain. The PET-MR scanner consists of a combined magnetic resonance imaging (MRI) magnet and a positron emission tomography (PET) imager. PET-MR allows investigators to look at a group of cells in the brain called 'microglia,' which are involved in inflammation and might be overactive in people who have migraine. Inflammation is a response of body tissues to injury or irritation. We would like to find out how a combination intervention of stress reduction training and tVNS in migraine patients might affect blood flow to different parts of the brain and/or inflammation in the brain.

Who will take part in this research?

We are asking you to take part in this study because you have recurrent episodes of migraine. About 150 participants will take part in this study at Massachusetts General Hospital (MGH) and Cambridge Health Alliance (CHA).

The NIH-NCCAM National Center for Complementary and Alternative Medicine [DHHS] and the Korea Institute of Oriental Medicine are paying for this research to be done.

What will happen in this research study?

If you choose to take part in this study, we will ask you to sign this consent form before we do any study procedures.

Visit 1: Eligibility Assessment and Consent

Today's visit is a screening visit to see if you might be eligible to participate in this study. It may take up to 2 hours. We will first go over this consent form and the study procedures.

During the rest of the visit, we may:

- Ask you to complete a medical history inventory and a physical examination with a nurse or a MD.

- Fill out questionnaires.

- Draw some blood (up to 10mL) or perform a saliva test to find out if the type of radioactive dye we will inject for the PET-MR scan will be appropriate for you. The dye that we use in this study cannot be seen very clearly in the body of some individuals. If we find out that this dye cannot be seen very well in your body, you may not be able to take part in the PET-MR part of this study. We will inform you of the result within 4 weeks of your first visit.

If you are still eligible after this visit, we will ask you to complete a daily online diary to report your experiences with migraine headache or aura for the duration of the study. These diaries are electronic and will available to you each day using a web-browser. If you are unable to complete the diaries electronically, paper copies will be provided. A texting application such as Twilio or Apptoto will be used to send participants reminders about appointment dates and times. It may also be used to remind participants about daily diary completion.

Do we have your permission to send text messages for scheduling, appointment, or daily diary reminders?
Yes No Initials_____

Visit 2: Behavioral Visit

The second study visit will be a behavioral testing visit. There will be no scans at this visit. It will take about 3 hours to complete.

During this visit, we may:
- Ask you to complete several electronic questionnaires about your symptoms.
- Monitor your heart rate, skin conductance, respiration, and blood pressure while we ask you to perform several tasks, including:

- A breathing task, where you will sit quietly and pace your breathing with a visual cue on a screen in front of you for 9 minutes.
- A sit-stand task, where we will ask you to stand from a seated position.
- Quantitative Sensory Testing, where you will go through several tests to measure your sensory responses. One type of sensory test will involve mechanical pressure applied to other parts of the body. You will tell the tester when you feel pain from each of the tests and you will rate the pain and other things you feel on a 0-100 rating scale. Another test will ask you to immerse your hand in cold water. You can stop any of the tests at any time.

Visit 3: fMRI Scan

The fMRI scanning visit will take approximately 3-4 hours, and you will be in the scanner for up to 2 hours. Prior to scanning, we will ask you to complete a safety questionnaire to ensure you do not have any contraindications to MRI scanning.

You will be placed in the MRI scanner and will lie quietly on a table that will slide inside a large magnet. A large plastic tube with holes in it will surround your head (this is the coil which transmits and collects radio wave signals). You will hear knocking sounds throughout the scan and you will be given earplugs to use to reduce the loud noises of the magnet. During the imaging session the investigators will be able to hear you while you are in the magnet. They will also be able to speak to you.

During the scan, we will ask you to complete several tasks, including:

- A forehead stimulation task, where electric stimulation will be applied to your forehead. The strength of stimulation will be set so as not to be painful.
- tVNS, which will include attaching electrodes to your ear after it is cleaned with alcohol. The strength of stimulation will be set so as not to be painful.
- A breath-hold task where you will hold your breath for 30 second intervals. You may notice that you are breathing deeper and more rapidly when you restore normal breathing after breath holding, but this is okay as we will monitor your breathing and make sure that your breathing is within safe limits. If the breathing procedures make you very uncomfortable, you can signal the study staff to stop the scan at any time.

Visit 4: PET-MR Scan

The PET-MR scanning visit may take 4-6 hours. Pregnant women cannot take part in this study and if you are a woman of childbearing age, blood will be drawn for a pregnancy test (up to 3mL) or we will ask you to provide a urine sample pregnancy test. During the visit, you will also be asked to provide a saliva sample for a toxicology screen. If the results of this test show the presence of drugs that were not previously disclosed and that could interfere with the trial (such

as substances of abuse) or with the PET scan, then you may be dropped from the study after consultation with a staff physician. The toxicology screen includes testing for the following kinds of drugs: alcohol, cocaine, cannabis, opioids (including oxycodone and fentanyl), amphetamines, methamphetamines, phencyclidine, benzodiazepines, barbiturates, and methadone. The results of the toxicology testing, while documented in the research records, will not be entered into your medical record/chart. If you qualify and want to continue to take part, we will place an intravenous (IV) catheter (a thin, flexible plastic tube with a needle attached) into a vein in your arm. During the PET-MR scan, we will inject a radioactive drug, called PBR28, through the IV catheter. This drug will travel through your blood stream. The PET scanner can see the radioactive drug and see how the different parts of your brain are working. Unless you have been previously genotyped for the Ala147Thr TSPO polymorphism (during the course of our previous experiments), either venous blood (up to 10 ml) or a saliva sample will be collected at the Screening for potential participation in a [^{11}C]PBR28 scan in order to have them genotyped for the Ala147Thr polymorphism in the TSPO gene (rs6971).

(We test your blood or saliva in Visit 1 to see if this drug will show up in your body.)

You will not be able to feel the radiation in your body. The radiation will quickly leave your body in your urine. During IV placement, blood may be drawn for further analysis.

We would also like your permission to place an arterial line ("A-line") into an artery in your wrist to draw blood samples throughout the scan, if the doctor or nurse practitioner has deemed it safe for us to do so. This procedure is optional for all subjects who qualify and you will still be able to participate in the study, even if you do not allow us to collect arterial blood. The collection of arterial blood allows us to measure how the radiotracer moves through your body, and we can use that information to get more accurate PET images.

The scan will be performed in either a head-only or full-body combination PET-MR scanner. The scanner is a very large magnet with a tunnel in the middle. During the PET-MR scan, you will be asked to lie still on your back on a narrow table that will slide into the tunnel-shaped machine. The machine is slightly wider than your body. The top and sides of the tunnel will be close to your face and body. This can make some people uncomfortable. If you have ever experienced a fear of small spaces (claustrophobia), please tell the staff.

In order to help hold your head still, we may place foam pillows under and around your head. The scanner makes loud banging and beeping noises when making pictures, so we will give you earplugs or headphones to protect your ears.

First, we will take some pictures of your brain. Then we will inject the radioactive drug into your IV catheter and take more pictures.

During the scan, we may ask you to look at pictures, listen to some sounds, or complete other tasks. You may also complete a task where you will be asked to focus on the sensation of your heart, lungs, sight, and sound. After focusing on these areas, you will be asked how strongly you felt each sensation. We will take pictures of your brain during these activities.

You will be able to hear and speak to the staff at all times during the procedure. If you become uncomfortable or want to stop the scan for any reason, just tell us and we will stop the scanning process immediately.

During the scan, you will be asked to complete a picture task where you will be asked to view a variety of pictures that have been categorized as either neutral or unpleasant. If any of the media presented should make you feel too uncomfortable to continue with the study, you are free to immediately withdraw your participation and leave without giving up credit or payment. To be clear: you may immediately end your participation if any aspect of the research procedure makes you too uncomfortable to continue.

After the scan is complete, you will sit up slowly and we will remove your catheter(s). After the removal of the arterial line we will observe you for up to one hour. In this period, we may ask you to complete another task where you watch dots moving on a screen and you will be asked to make responses on a keyboard based on the direction of their movement. After this period of observation, you are free to leave. Somebody from the study staff will call/email you the day following each scan to make sure that you are not experiencing any study related symptoms. Of course, you can contact us at any time if you have questions (see contact information under “If I have questions or concerns about this research study, whom can I call?”).

During the first four and final three visits we will also ask you to fill out different questionnaires.

If you decide to take part in the PET study, we will ask you not to take Sumatriptan or ergotamine related drugs such as dihydroergotamine or Cafergot 72 hours before the PET visit. If you need to use these kinds of medications within 72 hours prior to the PET visit, we ask that you inform us immediately so that we can reschedule your visit to a later date. While other medications such as over-the-counter pain medications are allowed, we ask that you report to us any medications you take 72 hours prior to the PET visit.

Visits 5-20: Treatment according to random assignment of treatment group
The stress reduction program consists of two types of training visits per week for 8 weeks and one 4-hour retreat. The first type of visit will consist of 8 weekly 90-minute training sessions with a small group led by an instructor. The second type of visit will include twice a week “booster” sessions with a 30-minute recording. You will have the option to participate in an intervention

which will include in-person/online "booster" sessions twice a week and a weekly virtual group visit. The virtual group sessions will take place on Zoom, a secure video call application. During both "booster" sessions, we will also use an active or inactive tVNS electrical stimulation device attached to your ear.

During the Stress Reduction Training, you will be asked to engage in at least 40-60 minutes of home practice for 4 out of 7 days of the week. You will not be asked to practice on the days you would have visits. You will document your home practice on your daily diaries. During the first "booster" session, a study staff member will review the device with you including safe and proper usage. The first day of home practice, you will connect with a study staff member via telephone/Zoom to help answer any questions. We also encourage you to have someone at home with you during the first session. You can also contact staff at any point during home practice sessions.

Parts of these treatment sessions will be recorded on videotape to check for consistency across different treatment groups. These videotapes will not have your name or any other identifiable information stored with them, and they will be destroyed 36 months after the study ends. No video recordings will be shared with anyone except study personnel.

Do you consent to being filmed during the treatment sessions?

Yes No Initials_____

You will complete morning and evening daily diaries throughout the duration of the study to report your experiences with migraine headache. These diaries will be available to you each day.

On some of the days you visit for a "booster" session, we will ask you to wear one sensor near your heart and one on your right leg. The sensor device is a BioStamp nPoint- a soft, flexible, water resistant patch approximately the size of a Band-aid. It has two electrodes, an accelerometer and a gyroscope. The BioStamp nPoint devices are very similar to an exercise activity tracker you might wear on your wrist; however, you will be asked to wear one of them on your skin just under the left collar bone and chest area like a sticker. You will be asked to wear the devices during the session, and then to take them home and wear them and reapply them at certain times on your own, until you are asked to return them later in the week at the Group session. The BioStamp nPoint is Bluetooth-enabled, meaning it can wirelessly communicate with a computer, once the device is taken off you; the device has a rechargeable battery. The BioStamp nPoint has been cleared by the FDA for sale in the USA and use by researchers and healthcare professionals.

At the first and last booster session, you will be asked to complete a task where you sit quietly and count your heartbeat. While you count, you will be asked to place your hands on a small device that monitors your heartbeat. This task will last 5 minutes.

Visits 21-23: Repeat Behavioral, fMRI scan, and PET-MR scan visits

After you complete treatment, we will repeat the same procedures performed during visits 2, 3, and 4. We will also ask you to complete follow-up questionnaires online at 3- or 6-months after these visits, but will not require you to visit us in person again.

COVID-19 Visit Changes

During this study we may need to make changes to study visits and procedures to comply with public health efforts to address COVID- 19 (coronavirus). We may need to adjust the study visit schedule and/or research procedures as a result of study site restrictions on research visits. We may conduct some study visits or select research procedures remotely until the restrictions are lifted. Remote visits will be conducted by secure video call or phone call.

For all study procedures conducted via video call, study staff will provide you information on how to access the video conferencing platform. We will launch the video conferencing in a private and secure area. To protect your privacy, we ask that you do not take screenshots, photographs, or recordings of any kind with any electronic equipment.

We would like to remind you that a video meeting is similar to us visiting you at home. We may learn more about your home and the people living with you than we would during a visit at the hospital. For example, we may learn information from you that must be reported to public health or public safety authorities. We are required by law to report known or suspected child or elder abuse. If we make such report, the public health and safety authorities can use the information as they see fit and may end up sharing it with other government agencies. Please ask the research staff if you have any questions about this prior to your video visit.

How may we use and share your samples and health information for other research?

The information we collect in this study may help advance other research. If you join this study, we may remove all information that identifies you (for example, your name, medical record number, and date of birth) and use these de-identified samples and data in other research. It won't be possible to link the information or samples back to you. Information and/or samples may be shared with investigators at our hospitals, at other academic institutions or at for-profit, commercial entities. You will not be asked to provide additional informed consent for these uses. A notation that you are taking part in this research study may be made in your electronic medical

record. Information from the research that relates to your general medical care may be included in the record (for example, list of allergies, results of standard blood tests done at the hospital labs).

At the completion of this research study, we would like to store and be able to use and share your identifiable samples and health information with researchers at MGB for other research related to neuroinflammation. We want to test blood levels of factors that may affect our interpretation of the imaging signal, including blood levels of hormones such as prolactin, estrogen and progesterone, pro- and anti-inflammatory mediators such as IL-6, IL-1b, TNF-alpha and IL-10, cell counts (such as monocyte / macrophage count), etc. If we share your samples and/or health information with other researchers outside of MGB, we will label the samples and information with a code instead of your name or other directly identifying information. The key to the code connects your name or other identifiers to your sample and/or information. We will keep the code in a password protected computer/locked file. Because these samples and/or health information are identifiable, we are asking your permission to store, use and share them for other research. You can still take part in the research study whether or not you give permission for the storage, use, and sharing of the samples and health information for other research.

Do you agree to let us store and use your samples and health information for other research related to chronic pain?

Yes No Initials_____

Will you get the results of this research study?

No. The research study we are doing is only a stepping stone in understanding chronic pain. Therefore, no information about the results of this research study or the results of your individual participation in the research study will be given to you or your doctor. Tests done for the research using your samples will not be useful in directing your medical treatment. The results of the tests will not be placed in your medical record.

What are the risks and possible discomforts from being in this research study?

Risks of MRI Scans
MRIs use powerful magnets to make images. There are no known radiation risks associated with MRI. However, persons with metal implants, such as surgical clips, or pacemakers should not have an MRI. All credit cards and other items with magnetic strips should also be kept out of the MRI room. People who feel uncomfortable in confined spaces (claustrophobia) may feel

uncomfortable in the narrow tube. The MRI makes loud banging noises as it takes images. Earplugs can be used to reduce the noises. The MRI can be stopped at any time at your request. If you are or suspect you are pregnant, you should not participate in this study. The MRI has the potential, during normal routine use, to cause localized warming of your skin and the underlying tissues. You should immediately inform us if you experience discomfort due to warming and the procedure will be stopped.

Some people experience dizziness or rarely nausea when going into an MRI scanner and these sensations may be more common in scans with higher magnetic fields. In most cases, these symptoms only last a short time. However, some people may experience them throughout the scan and/or continue to experience them for a short period of time after; generally, less than half an hour. No case of permanent problems is known.

Risks of Stress Reduction Training
Some individuals may become distressed as a result of the training. Your instructor will give you more information during the training. If you feel stressed at any time during the study, you may contact your instructor who may be able to assist you. You will be given their contact information at the start of the course.

Risks of tVNS
There are few known side effects of tVNS. Some people may get light headed. Please let us know if you feel light headed, and we will stop the session and remove the electrodes. The electrodes that are placed on your ear and attached to the stimulator are covered in silicone. Therefore, there is no added risk to you. Study staff will train you on how to use the device for home practice at the first "booster" session and will be available by phone or email in case you have any questions. You will also be given a device manual for reference throughout the home practice.

Risks of Breath-hold task
Side effects from holding your breath can include shortness of breath or light-headedness. Some people may have increase in heart rate, blood pressure and dizziness. If these side effects occur, they usually disappear within a few minutes of stopping holding your breath.

Risks of Sensory Testing
There may be increased pain from some of the sensory tests. The increased pain will usually decrease and go away within minutes. There is a slight chance of mild transient bruising associated with use of the probes or algometer. In our experience, this is quite rare (< 5 % of cases).

Skin Irritation risks
You will be asked to wear certain devices on your body throughout the study for monitoring and

stimulation purposes. The electrode gel used to apply these devices may cause minor skin irritation especially if you have sensitive skin. These issues would resolve within a few days.

Risks of refraining from migraine drugs prior to PET scan
If you choose not to take Sumatriptan or ergotamine related drugs such as dihydroergotamine or Cafergot 72 hours before the PET visit, please be aware that your headache pain may become worse and it may put you at an increased risk of discomfort. If your headache pain becomes worse and you need to use these kinds of medications within 72 hours prior to the PET visit, we will need to reschedule your visit to a later date. While other medications such as Tylenol and other over-the-counter pain medications are allowed, we ask that you report to us any medications you take 72 hours prior to the PET visit.

Risks of Radiation Exposure
As a result of your participation in this study you will be exposed to radiation from the PET scan of your brain. Please note that this radiation is not necessary for your medical care and is for research purposes only. The total amount of radiation exposure you will receive from being scanned for this study is equal to a whole body exposure of approximately 7.4 milliSieverts (mSv). A milliSievert is a unit of radiation dose. This amount of radiation is about the same as you would normally receive in 28 months from natural background sources from the earth and the sky. Scientists disagree on whether radiation doses at these low levels are harmful. A possible effect that could occur at doses associated with this study is a slight increase in the risk of developing cancer later in life.

If you are pregnant or breast feeding, you are not able to participate in this research study.

Since the effects of radiation can be cumulative, it is important to know of your past research related radiation exposure. If you have participated in other research studies in the past 12 months that have involved radiation exposure please inform the investigators or study staff. If it is determined that your prior radiation exposure exceeds our current guidelines, it is possible that you will not be allowed to participate in this study.

I have _____ have not_____ participated in research studies involving radiation exposure within the last 12 months.

Signature: _____

Risks to an Embryo or Fetus
Radiation exposure may be harmful to an embryo or fetus (developing baby still in the womb) or to a nursing infant. Because of these risks, you cannot be in this study if you are pregnant or nursing.

If you are a menopausal woman and have not had a period for the past 12 months or more, you will not need to have a pregnancy test. Also, you will not need to have a pregnancy test if you have had a hysterectomy (surgical removal of your uterus and/or ovaries). All other female subjects must have a negative blood or urine sample pregnancy test before having the MRI/PET scan.

Incidental Findings
We are doing the MR-PET scan in this study to answer research questions, not as part of your medical care. The information from this study will not usually become part of your hospital record. This MR-PET scan is not the same as the one that your doctor would order. It may or may not show problems that would be found on a standard MRI or PET scan. This type of scan is considered experimental. If we do see something that looks like a medical problem, we will ask a radiologist (a doctor who specializes in test results of this sort) to review the results. If the radiologist thinks that you might have a medical problem, we will tell you and help you get follow-up care. If the radiologist thinks that you might have a medical problem, but it turns out that you don't, we may have caused you to worry needlessly about your health.

Risks of the IV Catheter
Placing the IV catheter into your arm may cause some pain, bruising, bleeding, a slight risk of infection, and possibly fainting.

Risks of A-Line
Inserting an arterial line (A-line) can hurt more than having a regular IV or having blood drawn with a needle. We will place the A-line under local anesthesia (i.e., lidocaine), which may cause an allergic reaction. Even if we numb the wrist area first, the insertion may still hurt. Once the A-line is in place, it usually does not hurt.

Having an arterial line placed may cause:

- Pain, bleeding, swelling, or redness at the wrist. Rarely (less than 1 in 100), an infection may occur, which can be treated.
- Short loss of pulse at the wrist, if blood flow in the artery is briefly stopped (for example, because of a clot or spasm of the artery).
- Damage to the artery wall or nearby nerves.

Catheter breaking or falling out. There have been reports of decreased blood flow to the hand that resulted in the need for surgery. This is very rare and has not been reported when catheters have been in place for only a few hours for research.

After we remove the catheter:

- We will ask you to stay at least 30-minutes so that we can check that the site is healing properly.
- You may have a bruise or feel tenderness for 2-3 days around the area where the arterial line was placed.
- You should avoid lifting anything heavier than a small bag of flour for a day following the scan.

Call us if:

- Bleeding occurs after you leave (rare). Apply pressure to the site and go to the Emergency Department.
- The wrist area is painful, red, or swollen

Risks of Numbing Drug (Lidocaine)
An individual with anesthesia training will use lidocaine to numb your wrist area prior to placing the A-line. Risks of lidocaine include dizziness, nausea, drowsiness, ringing in the ears, numbness, or allergic reaction. An allergic reaction to lidocaine was observed in a very limited number of cases.

Risks of blood draws
The risks associated with having blood drawn include: bruising, local discomfort, or infection at the site of the needle puncture. Rarely an infection may occur at this site, and if an infection does occur, it will be treated.

The amount of blood that will be drawn for the study includes:

- Up to 10mL of blood may be drawn for genotyping at the screening visit.
- Up to 3mL of blood may be drawn for the pregnancy test at each PET visit.
- Up to 15mL of blood may be drawn at each PET visit for sample testing.
- Up to 160mL of blood may be drawn if you choose to have an arterial line placement at each PET visit.

In total, up to 376 mL of blood may be drawn for all study procedures including the arterial line. If you choose not to have an arterial line, up to 56mL of blood may be drawn for all study procedures.

Virtual Group Visits
Video call risks include an increased expense from cellular carrier if you have a limited data plan and you rely on a mobile data, instead of home internet, for videoconferencing. All internet-based technology, like the mobile application, is open to eavesdropping. Because of this we have made every effort to reduce the chance of outside people gaining access to protected data. The

system is very secure with updated security protection technology, but you should understand no system is perfectly secure.

Confidentiality Risk
There is a small risk that your confidential medical information could be revealed or discovered by mistake (due to human error). However, safeguards are in place to minimize this risk. Information about your taking part in this study or the results won't be placed in your medical records. In addition, your study information will be coded and the key to the code will be kept in a separate, locked file. Your identity will not be revealed if we publish any of the study information.

Someone could identify you from the videotapes of the group treatment sessions. The videos will be stored in a secure electronic location which will not be connected to the internet. Your videotaped sessions will not contain identifiable information, such as your name, and will be coded with a study number instead. The key that connects your identifiable information with the study number will be kept in a separate, locked file. Only the study staff that needs to study the interaction with you and the physician will be authorized to view the videotapes. We will not share or publish any information in a way that will identify you. You are free to decline being video-taped, and you can still continue the study without this. The video tapes will in no way affect the medical care you get within MGB now or in the future.

Suicidality Risks
If at any time during the initial evaluation visit or at any of the stimulation sessions, you present significant depressive symptomatology or suicidal ideation we will refer you to a licensed clinician for proper clinical follow-up or if immediate medical attention is required we will consult with the Massachusetts General Hospital Acute Psychiatric Service.

What are the possible benefits from being in this research study?

You may or may not benefit from taking part in this study. However, there is a possibility that taking part in this study might result in finding a medical condition that you didn't know about. In this case, this information will be discussed with you and we will help provide you with a referral for follow-up care. By receiving stress reduction training or tVNS interventions you may benefit by learning more about your condition and how to cope with it.

What other treatments or procedures are available for my condition?

You do not have to take part in this study to be treated for migraine. Mindfulness meditation, progressive muscle relaxation, and psychoeducation are available outside of this research study. Other treatments are available for migraine including medications and other treatments that do

not include drugs. The study staff will discuss with you the benefits and risks of other treatments

Can I still get medical care within MGB if I don't take part in this research study, or if I stop taking part?

Yes. Your decision won't change the medical care you get within MGB now or in the future. There will be no penalty, and you won't lose any benefits you receive now or have a right to receive.

Taking part in this research study is up to you. You can decide not to take part. If you decide to take part now, you can change your mind and drop out later. We will tell you if we learn new information that could make you change your mind about taking part in this research study.

What should I do if I want to stop taking part in the study?

If you take part in this research study, and want to drop out, you should tell us. We will make sure that you stop the study safely. We will also talk to you about follow-up care, if needed.

Also, it is possible that we will have to ask you to drop out of the study before you finish it. If this happens, we will tell you why. We will also help arrange other care for you, if needed.

Will I be paid to take part in this research study?

You will be paid the following for your participation in our study:

- $15 total for the blood/saliva test to determine PBR28 affinity and for the screening visit given in the form of a check.
- $50 for each behavioral visit given in the form of a check.
- $1.00 will be earned towards a diary completion bonus for completion of each day's Daily Diaries given in the form of a check.
  - If you complete the diaries on at least 90% of the days throughout the study, you will receive all the money earned towards that bonus.
  - If you complete the diaries for between 75% and 90% of the days throughout the study, you will receive 50% of the money earned towards the bonus.
  - If you complete the diaries for between 50% and 75% of the days throughout the study, you will receive 30% of the money earned towards the bonus.
- $150 for each MR-PET scanning visit given in the form of a check.

- $50 for optional A-line at the MR-PET visit given in the form of a check.
- $100 for each MRI-only scanning visit given in the form of a check.
- $15 for the blood or urine test to detect pregnancy during the MR-PET visit (if the subject is female of childbearing age) given in the form of a check.
- $10 for each online group visit in the form of gift cards.
- $10 for each in-person/online booster visit in the form of gift cards.
- $10 for transportation costs for each in-person visit in the form of gift cards.
- $20 for the 4-hour retreat in the form of gift cards.
- $20 for each follow-up visit (2 in total) in the form of gift cards.

In total, you may earn up to $1,330 if you complete all study visits and daily diaries. However, you may not be eligible for the MR-PET scanning visits or pregnancy tests. You will receive the payment in the form of a check from MGH and Amazon or Tango gift cards. Gift cards will be given out or emailed at the group sessions, the retreat, and the follow up visits.

If you do not already have a phone plan that works for virtual visits, we will also cover up to $80 dollars for wireless or Wi-Fi costs for the 8 weeks of the Stress Reduction Training. We would require a receipt or proper documentation.

If during the imaging visit(s) we use the radioligand (e.g., due to a failure in radiosynthesis, or to issues with the scanner), we may continue with the MRI data collection and you will receive $100.

If you do not complete the scanning visit for any reason, we will pay you $25 for your time. We will pay for your parking in the hospital garage during the study visit.

What will I have to pay for if I take part in this research study?

Study funds will pay for the fMRI and PET-MR scans and all the tests and procedures that are done only for the research.

Costs for any ongoing or routine medical care you would receive apart from this study will be billed to you or to your insurance company in the usual way. You will be responsible for any deductibles or co-payments required by your insurer.

How are your samples stored?

Study staff will assign your sample a code number and store it in a freezer. They will not keep your name or other information that could identify you with your sample. They will use the code number to connect your sample to your health information that is stored in a computer database. The computer database is protected with a password. Only study staff will know the password.

Which researchers can use your samples and what information about you can they have?

Your samples will be made available to researchers at MGH and other MGB institutions, as well as non-MGB academic institutions. Occasionally, your samples may be shared with for-profit companies that are working with MGH or other MGB researchers on a specific research project. Your samples will not be sold to anyone for profit. We will usually provide samples with limited information that does not directly identify you.

- As described above, all of the samples being stored are labeled with a code number that connects the sample to medical information related to the sample. The key to the code that links the samples and information to a specific individual will only be available to the study staff, and will be securely stored.
- Researchers at MGB institutions, whose studies have been approved by the hospital ethics board, may be allowed to review your medical record to collect more health information about you. The ethics board is a group that independently reviews and watches over all research studies involving people. The board follows state and federal laws and codes of ethics to make sure that the rights and welfare of people taking part in research studies are protected.
- Researchers outside of MGH will not be given the key to the code that links your sample and medical information to your name or other direct identifiers.

For what type of research will my samples be used?

Your samples and information will be used mainly to understand pain disorders. The long-term goals of the research are to learn how to better understand, prevent, diagnose or treat chronic pain. It is not possible to list every research project. Also, we cannot predict all of the research questions that will be important over the next years. As we learn more, there are new research questions and new types of research related to pain disorders may be done.

We plan to do genetic research on the DNA in your sample. DNA is the material that makes up your genes. All living things are made of cells. Genes are the part of cells that contain the instructions which tell our bodies how to grow and work, and determine physical characteristics such as hair and eye color. Genes are passed from parent to child.

How long will my samples and information be kept?

There is no scheduled date on which your samples and information in the bank will be destroyed. Your samples may be stored for research until they are "used up."

Can I stop allowing my samples and information to be stored and used for research?

Yes. You have a right to withdraw your permission at any time. If you do, your samples and information will be destroyed. However, it will not be possible to destroy samples and information that have already been given to researchers. If you decide to withdraw your permission, you should contact Dr. Loggia.

What happens if I am injured as a result of taking part in this research study?

We will offer you the care needed to treat any injury that directly results from taking part in this research study. We reserve the right to bill your insurance company or other third parties, if appropriate, for the care you get for the injury. We will try to have these costs paid for, but you may be responsible for some of them. For example, if the care is billed to your insurer, you will be responsible for payment of any deductibles and co-payments required by your insurer.

Injuries sometimes happen in research even when no one is at fault. There are no plans to pay you or give you other compensation for an injury, should one occur. However, you are not giving up any of your legal rights by signing this form.

If you think you have been injured or have experienced a medical problem as a result of taking part in this research study, tell the person in charge of this study as soon as possible. The researcher's name and phone number are listed in the next section of this consent form.

If I have questions or concerns about this research study, whom can I call?

You can call us with your questions or concerns. Our telephone numbers are listed below. Ask questions as often as you want.

Vitaly Napadow, PhD is the person in charge of this research study. You can call him at 617-724-3402, M-F 9-5. For questions regarding PET-MR imaging you can also call Nouchine Hadjikhani, MD, PhD at 617-724-5625, M-F 9-5, and Marco Loggia, PhD at 617- 643-7267 with questions about this research study.

If you have questions about the scheduling of appointments or study visits, email MigraineRelief@mgb.org or call the Research Coordinator at 617-952-6481.

If you want to speak with someone **not** directly involved in this research study, please contact the MGB Human Research Committee office. You can call them at 857-282-1900.

You can talk to them about:

- Your rights as a research subject
- Your concerns about the research
- A complaint about the research

Also, if you feel pressured to take part in this research study, or to continue with it, they want to know and can help.

If I take part in this research study, how will you protect my privacy?

Federal law requires MGB to protect the privacy of health information and related information that identifies you. We refer to this information as "identifiable information."

In this study, we may collect identifiable information about you from:

- Past, present, and future medical records
- Research procedures, including research office visits, tests, interviews, and questionnaires

Who may see, use, and share your identifiable information and why:

- MGB researchers and staff involved in this study
- The sponsor(s) of the study, and people or groups it hires to help perform this research or to audit the research
- Other researchers and medical centers that are part of this study
- The MGB ethics board or an ethics board outside MGB that oversees the research
- A group that oversees the data (study information) and safety of this study

- Non-research staff within MGB who need identifiable information to do their jobs, such as for treatment, payment (billing), or hospital operations (such as assessing the quality of care or research)
- People or groups that we hire to do certain work for us, such as data storage companies, accreditors, insurers, and lawyers
- Federal agencies (such as the U.S. Department of Health and Human Services (DHHS) and agencies within DHHS like the Food and Drug Administration, the National Institutes of Health, and the Office for Human Research Protections) state agencies, and foreign government bodies that oversee, evaluate, and audit research, which may include inspection of your records
- Public health and safety authorities, if we learn information that could mean harm to you or others (such as to make required reports about communicable diseases or about child or elder abuse)
- Other researchers within or outside MGB, for use in other research as allowed by law.

Certificate of Confidentiality

A federal Certificate of Confidentiality (Certificate) has been issued for this research to add special protection for information and specimens that may identify you. With a Certificate, unless you give permission (such as in this form) and except as described above, the researchers are not allowed to share your identifiable information or identifiable specimens, including for a court order or subpoena.

Certain information from the research will be put into your medical record and will not be covered by the Certificate. This includes records of medical tests or procedures done at the hospitals and clinics, and information that treating health care providers may need to care for you. Please ask your study doctor if you have any questions about what information will be included in your medical record. Other researchers receiving your identifiable information or specimens are expected to comply with the privacy protections of the Certificate. The Certificate does not stop you from voluntarily releasing information about yourself or your participation in this study.

Even with these measures to protect your privacy, once your identifiable information is shared outside MGB, we cannot control all the ways that others use or share it and cannot promise that it will remain completely private.

Because research is an ongoing process, we cannot give you an exact date when we will either destroy or stop using or sharing your identifiable information. Your permission to use and share your information does not expire.

The results of this research may be published in a medical book or journal, or used to teach others. However, your name or other identifiable information **will not** be used for these purposes without your specific permission.

Your Privacy Rights

You have the right **not** to sign this form that allows us to use and share your identifiable information for research; however, if you don't sign it, you can't take part in this research study.

You have the right to withdraw your permission for us to use or share your identifiable information for this research study. If you want to withdraw your permission, you must notify the person in charge of this research study in writing. Once permission is withdrawn, you cannot continue to take part in the study.

If you withdraw your permission, we will not be able to take back information that has already been used or shared with others, and such information may continue to be used for certain purposes, such as to comply with law or maintain the reliability of the study.

You have the right to see and get a copy of your identifiable information that is used or shared for treatment or for payment. To ask for this information, please contact the person in charge of this research study. You may only get such information after the research is finished.

Research Consent to Receive Unencrypted Text Message Communications

Text messages by mobile/cell phones are a common form of communication. The Migraine Relief research study involves sending you text messages that are relevant to the research study. Texting over mobile/cell phones carries security risks because text messages to mobile/cell phones are not encrypted. This means that information you send or receive by text message could be intercepted or viewed by an unintended recipient, or by your mobile/cell phone provider or carrier.

Below are some important points about texting in this research study.

- Text messages are not encrypted, and therefore carry security risks. This research study and Mass General Brigham are not responsible for any interception of messages sent through unencrypted text message communications.
- You will be responsible for all fees charged by your carrier's service plan for text messaging. This research study and Mass General Brigham are not responsible for any

increased charges, data usage against plan limits or changes to data fees from the research texts.

- Text messages will only be read during regular business hours. Texts sent on nights or weekends will not be read until the following business day.
- Text messaging should not be used in case of an emergency. If you experience a medical emergency, call 911 or go to the nearest hospital emergency department.
- You may decide to not send or receive text messages with staff associated with this research study at any time. You can do this in person or by contacting the Research Coordinator via email or phone.
- Your agreement applies to this research study only. Agreeing to other texts from Mass General Brigham, for example appointment reminders, is a separate process. Opting out of other texts from Mass General Brigham is a separate process as well.
- It is your responsibility to update your mobile/cell phone number with this research study in the event of a change.

I have had the chance to ask questions about texting with staff associated with this research study. I have been informed of the risks and other information covered above and consent to the use of unencrypted text communications associated with this research study.

Do we have your permission to send text messages for scheduling, appointment, or daily diary reminders?
Yes No Initials_____

Informed Consent and Authorization

Statement of Person Giving Informed Consent and Authorization

- I have read this consent form.
- This research study has been explained to me, including risks and possible benefits (if any), other possible treatments or procedures, and other important things about the study.
- I have had the opportunity to ask questions.
- I understand the information given to me.

Study Options

PET-MR with A-Line ☐ PET-MR without A-line ☐ MR only ☐

Do you agree participate in the PET-MR portions of the study?

Yes No Initials_____

If yes, do you agree to have an A-line placed during the PET-MR portions of the study?

Yes No Initials_____

Signature of Subject:

I give my consent to take part in this research study and agree to allow my health information to be used and shared as described above.

_____
Print Name

_____ _____ _____
Subject Date Time

Signature of Study Doctor or Person Obtaining Consent:

Statement of Study Doctor or Person Obtaining Consent

- I have explained the research to the study subject.
- I have answered all questions about this research study to the best of my ability.

_____
Print Name

_____ _____ _____
Study Doctor or Person Obtaining Consent Date Time

Consent Form Version Date: April 22nd, 2024

MGB HealthCare System
Research Consent Form

Subject Name:
MRN or DOB:
Subject Identification

Certificate of Confidentiality Template
Version Date: January 2018

Protocol Title: Brain mechanisms of vagus nerve stimulation and stress reduction training for migraine

Principal Investigator: Vitaly Napadow, PhD

Site Principal Investigator:

Description of Subject Population: Healthy Volunteers

About this consent form

Please read this form carefully. It tells you important information about a research study. A member of our research team will also talk to you about taking part in this research study. People who agree to take part in research studies are called "subjects." This term will be used throughout this consent form.

MGB HealthCare System is made up of MGB hospitals, health care providers, and researchers.

If you have any questions about the research or about this form, please ask us. Taking part in this research study is up to you. If you decide to take part in this research study, you must sign this form to show that you want to take part. We will give you a signed copy of this form to keep.

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov,* as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Why is this research study being done?

In this research study we want to learn more about migraines.

Dr. Napadow, the Principal Investigator on this study, is an inventor of technology that is used in this study. The hospital owns this technology and therefore Dr. Napadow and the hospital may benefit financially if this study shows that the technology is valuable. The hospital's conflict of interest policies are handled by the hospital's owner, MGB HealthCare. In accordance with these policies, MGB has determined that the interests create no significant risk to the welfare of participants in this study or to the integrity of the research. If you want more information about this, please contact the MGB Office for Interactions with Industry at 857-282-2024.

How long will I take part in this research study?

As a part of this study, we will ask you to come to the Charlestown Navy Yard campus of MGH for 4 visits. Additionally, we will ask you to complete daily diaries of any pain symptoms up until your second visit. These diaries are electronic and will available to you each day using a web-browser.

It will take about 7 weeks to complete the study.

The NIH-NCCAM National Center for Complementary and Alternative Medicine [DHHS] and the Korea Institute of Oriental Medicine are paying for this research to be done.

What will happen in this research study?

If you decide to join this research study, the following things will happen including personal health tracking, surveys, blood draws, an injection and IV placement, MRI scans, PET scans, and office visits.

Why might you choose to take part in this study?

We cannot promise any benefits to you from taking part in this research study. People with chronic pain conditions may benefit in the future from what we learn in this study.

Why might you choose NOT to take part in this study?

Taking part in this research study has some risks and requirements that you should consider carefully. A detailed description of all side effects, risks, and possible discomforts can be found later in this consent form in the section called “What are the risks and possible discomforts from being in this research study?” Other things to consider are the time commitment and travel requirements to the Charlestown Navy Yard and the Cambridge Health Alliance.

Detailed Information

Why is this research study being done?

The purpose of this study is to explore how a stress reduction program to help manage migraine, in conjunction with brief stimulation of the vagus nerve using a procedure called tVNS, affect the brains of migraine patients. This study uses two types of brain imaging to understand these effects. Functional MRI (fMRI) scan can take detailed pictures of the brain and a Positron Emission Tomography (PET) scan allows us to see areas of the brain exhibiting inflammation. The fMRI allows investigators to evaluate changes in how blood flows to parts of your brain. The PET-MR scanner consists of a combined magnetic resonance imaging (MRI) magnet and a positron emission tomography (PET) imager. PET-MR allows investigators to look at a group of cells in the brain called 'microglia,' which are involved in inflammation and might be overactive in people who have migraine. Inflammation is a response of body tissues to injury or irritation. We would like to find out how a combination intervention of stress reduction training and tVNS in migraine patients might affect blood flow to different parts of the brain and/or inflammation in the brain.

Who will take part in this research?

We are asking you to take part in this study because you are a healthy volunteer. About 50 healthy volunteer participants will take part in this study at Massachusetts General Hospital (MGH).

The NIH-NCCAM National Center for Complementary and Alternative Medicine [DHHS], the NIH-OD Office of the Director, and the Korea Institute of Oriental Medicine are paying for this research to be done.

What will happen in this research study?

If you choose to take part in this study, we will ask you to sign this consent form before we do any study procedures.

Visit 1: Eligibility Assessment and Consent

Today's visit is a screening visit to see if you might be eligible to participate in this study. It may take up to 2 hours. We will first go over this consent form and the study procedures.

During the rest of the visit, we may:

- Ask you to complete a medical history inventory and a physical examination with a nurse or a MD.

- Fill out questionnaires.

- Draw some blood (up to 10mL) or perform a saliva test to find out if the type of radioactive dye we will inject for the PET-MR scan will be appropriate for you. The dye that we use in this study cannot be seen very clearly in the body of some individuals. If we find out that this dye cannot be seen very well in your body, you may not be able to take part in the PET-MR part of this study. We will inform you of the result before scheduling any visits.

If you are still eligible after this visit, we will ask you to complete a daily online diary to report your experiences with any pain until your second visit. These diaries will be emailed to you or available on the web each day. If you are unable to complete the diaries electronically, paper copies will be provided.

Visit 2: Behavioral Visit

The second study visit will be a behavioral testing visit. There will be no scans at this visit. It will take about 2-3 hours to complete.

During this visit, we may:

- Ask you to complete several electronic questionnaires about your symptoms.
- Monitor your heart rate, skin conductance, respiration, and blood pressure while we ask you to perform several tasks, including:
    - A breathing task, where you will sit quietly and pace your breathing with a visual cue on a screen in front of you for 9 minutes.
    - A sit-stand task, where we will ask you to stand from a seated position.
    - Quantitative Sensory Testing, where you will go through several tests to measure your sensory responses. One type of sensory test will involve mechanical pressure applied to other parts of the body. You will tell the tester when you feel pain from each of the tests and you will rate the pain and other things you feel on a 0-100 rating scale. Another test will ask you to immerse your hand in cold water. You can stop any of the tests at any time.

Visit 3: fMRI Scan

The fMRI scanning visit will take approximately 3-4 hours, and you will be in the scanner for up to 2 hours. Prior to scanning, we will ask you to complete a safety questionnaire to ensure you do not have any contraindications to MRI scanning.

You will be placed in the MRI scanner and will lie quietly on a table that will slide inside a large magnet. A large plastic tube with holes in it will surround your head (this is the coil which transmits and collects radio wave signals). You will hear knocking sounds throughout the scan and you will be given earplugs to use to reduce the loud noises of the magnet. During the imaging session the investigators will be able to hear you while you are in the magnet. They will also be able to speak to you.

During the scan, we will ask you to complete several tasks, including:

- A forehead stimulation task, where electric stimulation will be applied to your forehead. The strength of stimulation will be set so as not to be painful.
- tVNS, which will include attaching electrodes to your ear after it is cleaned with alcohol. The strength of stimulation will be set so as not to be painful.
- A breath-hold task where you will hold your breath for 30 second intervals. You may notice that you are breathing deeper and more rapidly when you restore normal breathing after breath holding, but this is okay as we will monitor your breathing and make sure that your breathing is within safe limits. If the breathing procedures make you very uncomfortable, you can signal the study staff to stop the scan at any time.

Visit 4: PET-MR Scan

The PET-MR scanning visit may take 4-6 hours**.** Pregnant women cannot take part in this study and if you are a woman of childbearing age, blood will be drawn for a pregnancy test (up to 3mL) or a urine sample pregnancy test will be performed. During the visit, you will also be asked to provide a saliva sample for a toxicology screen. If the results of this test show the presence of drugs that were not previously disclosed and that could interfere with the trial (such as substances of abuse) or with the PET scan, then you may be dropped from the study after consultation with a staff physician. The toxicology screen includes testing for the following kinds of drugs: alcohol, cocaine, cannabis, opioids (including oxycodone and fentanyl), amphetamines, methamphetamines, phencyclidine, benzodiazepines, barbiturates, and methadone. The results of the toxicology testing, while documented in the research records, will not be entered into your medical record/chart. If you qualify and want to continue to take part, we will place an intravenous (IV) catheter (a thin, flexible plastic tube with a needle attached) into a vein in your arm. During the PET-MR scan, we will inject a radioactive drug, called PBR28, through the IV catheter. This drug will travel through your blood stream. The PET scanner can see the radioactive drug and see how the different parts of your brain are working. Either venous blood (up to 10 ml) or a saliva sample will be collected at the Screening Visit from you if you are considered for potential participation in a [^{11}C]PBR28 scan in order to have them genotyped for the Ala147Thr polymorphism in the TSPO gene (rs6971).

(We test your blood or saliva in Visit 1 to see if this drug will show up in your body.)

You will not be able to feel the radiation in your body. The radiation will quickly leave your body in your urine. During IV placement, blood may be drawn for further analysis.

We would also like your permission to place an arterial line ("A-line") into an artery in your wrist to draw blood samples throughout the scan, if the doctor or nurse practitioner has deemed it safe for us to do so. This procedure is optional for all subjects who qualify and you will still be able to participate in the study, even if you do not allow us to collect arterial blood. The collection of arterial blood allows us to measure how the radiotracer moves through your body, and we can use that information to get more accurate PET images.

The scan will be performed in either a head-only or full-body combination PET-MRI scanner. The scanner is a very large magnet with a tunnel in the middle. During the PET-MR scan, you will be asked to lie still on your back on a narrow table that will slide into the tunnel-shaped machine. The machine is slightly wider than your body. The top and sides of the tunnel will be close to your face and body. This can make some people uncomfortable. If you have ever experienced a fear of small spaces (claustrophobia), please tell the staff.

In order to help hold your head still, we may place foam pillows under and around your head. The scanner makes loud banging and beeping noises when making pictures, so we will give you earplugs or headphones to protect your ears.

First, we will take some pictures of your brain. Then we will inject the radioactive drug into your IV catheter and take more pictures.

During the scan, we may ask you to look at pictures, listen to some sounds, or complete other tasks**.** You may also complete a task where you will be asked to focus on the sensation of your heart, lungs, sight, and sound. After focusing on these areas, you will be asked how strongly you felt each sensation. We will take pictures of your brain during these activities.

You will be able to hear and speak to the staff at all times during the procedure. If you become uncomfortable or want to stop the scan for any reason, just tell us and we will stop the scanning process immediately.

During the scan, you will be asked to complete a picture task where you will be asked to view a variety of pictures that have been categorized as either neutral or unpleasant. If any of the media presented should make you feel too uncomfortable to continue with the study, you are free to immediately withdraw your participation and leave without giving up credit or payment. To be clear: you may immediately end your participation if any aspect of the research procedure makes you too uncomfortable to continue.

After the scan is complete, you will sit up slowly and we will remove your catheter(s). After the removal of the arterial line we will observe you for up to one hour. In this period, we may ask you to complete another task where you watch dots moving on a screen and you will be asked to make responses on a keyboard based on the direction of their movement. After this period of

observation, you are free to leave. Somebody from the study staff will call/email you the day following each scan to make sure that you are not experiencing any study related symptoms. Of course, you can contact us at any time if you have questions (see contact information under "If I have questions or concerns about this research study, whom can I call?").

During these four visits we will also ask you to fill out questionnaires.

COVID-19 Visit Changes

During this study we may need to make changes to study visits and procedures to comply with public health efforts to address COVID- 19 (coronavirus). We may need to adjust the study visit schedule and/or research procedures as a result of study site restrictions on research visits. We may conduct some study visits or select research procedures remotely until the restrictions are lifted. Remote visits will be conducted by secure video call or phone call.

For all study procedures conducted via video call, study staff will provide you information on how to access the video conferencing platform. We will launch the video conferencing in a private and secure area. To protect your privacy, we ask that you do not take screenshots, photographs, or recordings of any kind with any electronic equipment.

We would like to remind you that a video meeting is similar to us visiting you at home. We may learn more about your home and the people living with you than we would during a visit at the hospital. For example, we may learn information from you that must be reported to public health or public safety authorities. We are required by law to report known or suspected child or elder abuse. If we make such report, the public health and safety authorities can use the information as they see fit and may end up sharing it with other government agencies. Please ask the research staff if you have any questions about this prior to your video visit.

How may we use and share your samples and health information for other research?

The information we collect in this study may help advance other research. If you join this study, we may remove all information that identifies you (for example, your name, medical record number, and date of birth) and use these de-identified samples and data in other research. It won't be possible to link the information or samples back to you. Information and/or samples may be shared with investigators at our hospitals, at other academic institutions or at for-profit, commercial entities. You will not be asked to provide additional informed consent for these uses. A notation that you are taking part in this research study may be made in your electronic medical record. Information from the research that relates to your general medical care may be included in the record (for example, list of allergies, results of standard blood tests done at the hospital labs).

At the completion of this research study, we would like to store and be able to use and share your identifiable samples and health information with researchers at MGB for other research related to neuroinflammation. We want to test blood levels of factors that may affect our interpretation of the imaging signal, including blood levels of hormones such as prolactin, estrogen and progesterone, pro- and anti-inflammatory mediators such as IL-6, IL-1b, TNF-alpha and IL-10, cell counts (such as monocyte / macrophage count), etc. If we share your samples and/or health information with other researchers outside of MGB, we will label the samples and information with a code instead of your name or other directly identifying information. The key to the code connects your name or other identifiers to your sample and/or information. We will keep the code in a password protected computer/locked file. Because these samples and/or health information are identifiable, we are asking your permission to store, use and share them for other research. You can still take part in the research study whether or not you give permission for the storage, use, and sharing of the samples and health information for other research.

Do you agree to let us store and use your samples and health information for other research related to chronic pain?

Yes No Initials_____

Will you get the results of this research study?

No. The research study we are doing is only a stepping stone in understanding chronic pain. Therefore, no information about the results of this research study or the results of your individual participation in the research study will be given to you or your doctor. Tests done for the research using your samples will not be useful in directing your medical treatment. The results of the tests will not be placed in your medical record.

What are the risks and possible discomforts from being in this research study?

Risks of MRI Scans
MRIs use powerful magnets to make images. There are no known radiation risks associated with MRI. However, persons with metal implants, such as surgical clips, or pacemakers should not have an MRI. All credit cards and other items with magnetic strips should also be kept out of the MRI room. People who feel uncomfortable in confined spaces (claustrophobia) may feel uncomfortable in the narrow tube. The MRI makes loud banging noises as it takes images. Earplugs can be used to reduce the noises. The MRI can be stopped at any time at your request. If you are or suspect you are pregnant, you should not participate in this study. The MRI has the potential, during normal routine use, to cause localized warming of your skin and the underlying

tissues. You should immediately inform us if you experience discomfort due to warming and the procedure will be stopped.

Some people experience dizziness or rarely nausea when going into an MRI scanner and these sensations may be more common in scans with higher magnetic fields. In most cases, these symptoms only last a short time. However, some people may experience them throughout the scan and/or continue to experience them for a short period of time after; generally, less than half an hour. No case of permanent problems is known.

Risks of tVNS
There are few known side effects of tVNS. Some people may get light headed. Please let us know if you feel light headed, and we will stop the session and remove the electrodes. The electrodes that are placed on your ear and attached to the stimulator are covered in silicone. Therefore, there is no added risk to you.

Risks of Breath-hold task
Side effects from holding your breath can include shortness of breath or light-headedness. Some people may have increase in heart rate, blood pressure and dizziness. If these side effects occur, they usually disappear within a few minutes of stopping holding your breath.

Risks of Sensory Testing
There may be increased pain from some of the sensory tests. The increased pain will usually decrease and go away within minutes. There is a slight chance of mild transient bruising associated with use of the probes or algometer. In our experience, this is quite rare (< 5 % of cases). Electrode gel used for stimulation and monitoring may cause minor skin irritation that would resolve within a few days.

Risks of Radiation Exposure
As a result of your participation in this study you will be exposed to radiation from the PET scan of your brain. Please note that this radiation is not necessary for your medical care and is for research purposes only. The total amount of radiation exposure you will receive from being scanned for this study is equal to a whole body exposure of approximately 3.7 milliSieverts (mSv). A milliSievert is a unit of radiation dose. This amount of radiation is about the same as you would normally receive in 14 months from natural background sources from the earth and the sky. Scientists disagree on whether radiation doses at these low levels are harmful. A possible effect that could occur at doses associated with this study is a slight increase in the risk of developing cancer later in life.

If you are pregnant or breast feeding, you are not able to participate in this research study.

Since the effects of radiation can be cumulative, it is important to know of your past research

related radiation exposure. If you have participated in other research studies in the past 12 months that have involved radiation exposure, please inform the investigators or study staff. If it is determined that your prior radiation exposure exceeds our current guidelines, it is possible that you will not be allowed to participate in this study.

I have _____ have not_____ participated in research studies involving radiation exposure within the last 12 months.

Signature: _____

Risks to an Embryo or Fetus
Radiation exposure may be harmful to an embryo or fetus (developing baby still in the womb) or to a nursing infant. Because of these risks, you cannot be in this study if you are pregnant or nursing.

If you are a menopausal woman and have not had a period for the past 12 months or more, you will not need to have a pregnancy test. Also, you will not need to have a pregnancy test if you have had a hysterectomy (surgical removal of your uterus and/or ovaries). All other female subjects must have a negative blood or urine pregnancy test before having the PET-MR scan.

Incidental Findings
We are doing the MR-PET scan in this study to answer research questions, not as part of your medical care. The information from this study will not usually become part of your hospital record. This MR-PET scan is not the same as the one that your doctor would order. It may or may not show problems that would be found on a standard MRI or PET scan. This type of scan is considered experimental. If we do see something that looks like a medical problem, we will ask a radiologist (a doctor who specializes in test results of this sort) to review the results. If the radiologist thinks that you might have a medical problem, we will tell you and help you get follow-up care. If the radiologist thinks that you might have a medical problem, but it turns out that you don't, we may have caused you to worry needlessly about your health.

Risks of the IV Catheter
Placing the IV catheter into your arm may cause some pain, bruising, bleeding, a slight risk of infection, and possibly fainting.

Risks of A-Line
Inserting an arterial line (A-line) can hurt more than having a regular IV or having blood drawn with a needle. We will place the A-line under local anesthesia (i.e., lidocaine), which may cause an allergic reaction. Even if we numb the wrist area first, the insertion may still hurt. Once the A-line is in place, it usually does not hurt.

Having an arterial line placed may cause:

- Pain, bleeding, swelling, or redness at the wrist. Rarely (less than 1 in 100), an infection may occur, which can be treated.
- Short loss of pulse at the wrist, if blood flow in the artery is briefly stopped (for example, because of a clot or spasm of the artery).
- Damage to the artery wall or nearby nerves.

Catheter breaking or falling out. There have been reports of decreased blood flow to the hand that resulted in the need for surgery. This is very rare and has not been reported when catheters have been in place for only a few hours for research.

After we remove the catheter:

- We will ask you to stay for at least 30-minutes so that we can check that the site is healing properly.
- You may have a bruise or feel tenderness for 2-3 days around the area where the arterial line was placed.
- You should avoid lifting anything heavier than a small bag of flour for a day following the scan.

Call us if:

- Bleeding occurs after you leave (rare). Apply pressure to the site and go to the Emergency Department.
- The wrist area is painful, red, or swollen

Risks of Numbing Drug (Lidocaine)
An individual with anesthesia training will use lidocaine to numb your wrist area prior to placing the A-line. Risks of lidocaine include dizziness, nausea, drowsiness, ringing in the ears, numbness, or allergic reaction. An allergic reaction to lidocaine was observed in a very limited number of cases.

Risks of blood draws
The risks associated with having blood drawn include: bruising, local discomfort, or infection at the site of the needle puncture. Rarely an infection may occur at this site, and if an infection does occur, it will be treated.

The amount of blood that will be drawn for the study includes:

- up to 10mL of blood may be drawn for genotyping at the screening visit.
- up to 3mL of blood may be drawn for the pregnancy test at the PET visit.
- up to 15mL of blood may be drawn at the PET visit for sample testing.
- up to 160mL of blood may be drawn if you choose to have an arterial line placement at the

PET visit.

In total, up to 188 mL of blood may be drawn for all study procedures including the arterial line. If you choose not to have an arterial line, up to 38mL of blood may be drawn for all study procedures.

Confidentiality Risk
There is a small risk that your confidential medical information could be revealed or discovered by mistake (due to human error). However, safeguards are in place to minimize this risk. Information about your taking part in this study or the results won't be placed in your medical records. In addition, your study information will be coded and the key to the code will be kept in a separate, locked file. Your identity will not be revealed if we publish any of the study information.

What are the possible benefits from being in this research study?

You may not benefit from taking part in this study. However, there is a possibility that taking part in this study might result in finding a medical condition that you didn't know about. In this case, this information will be discussed with you and we will help provide you with a referral for follow-up care.

Can I still get medical care within MGB if I don't take part in this research study, or if I stop taking part?

Yes. Your decision won't change the medical care you get within MGB now or in the future. There will be no penalty, and you won't lose any benefits you receive now or have a right to receive.

Taking part in this research study is up to you. You can decide not to take part. If you decide to take part now, you can change your mind and drop out later. We will tell you if we learn new information that could make you change your mind about taking part in this research study.

What should I do if I want to stop taking part in the study?

If you take part in this research study, and want to drop out, you should tell us. We will make sure that you stop the study safely. We will also talk to you about follow-up care, if needed.

Also, it is possible that we will have to ask you to drop out of the study before you finish it. If this happens, we will tell you why. We will also help arrange other care for you, if needed.

Will I be paid to take part in this research study?

You will be paid the following for your participation in our study:

- $15 total for the blood/saliva test to determine PBR28 affinity and for the screening visit.
- $50 for the behavioral visit.
- $1.00 will be earned towards a diary completion bonus for completion of each day's Daily Diaries.
  - If you complete the diaries on at least 90% of the days throughout the study, you will receive all the money earned towards that bonus.
  - If you complete the diaries for between 75% and 90% of the days throughout the study, you will receive 50% of the money earned towards the bonus.
  - If you complete the diaries for between 50% and 75% of the days throughout the study, you will receive 30% of the money earned towards the bonus.
  - This amounts to a maximum of $28 for completing Diaries every day for four weeks.
- $150 for the MR-PET scanning visit.
- $50 for optional A-line at the MR-PET visit.
- $100 for the MRI-only scanning visit.
- $15 for the blood or urine test to detect pregnancy during the MR-PET visit (if the subject is female of childbearing age).

In total, you may earn up to $425 if you complete all study visits and daily diaries. However, you may not be eligible for the PET-MR scanning visits or pregnancy tests.

If during the imaging visit we use the radioligand (e.g., due to a failure in radiosynthesis, or to issues with the scanner), we may continue with the MRI data collection and you will receive $100.

If you do not complete the scanning visit for any reason, we will pay you $25 for your time. We will pay for your parking in the hospital garage during the study visit.

What will I have to pay for if I take part in this research study?

Study funds will pay for the fMRI and PET-MR scans and all the tests and procedures that are done only for the research.

Costs for any ongoing or routine medical care you would receive apart from this study will be billed to you or to your insurance company in the usual way. You will be responsible for any deductibles or co-payments required by your insurer.

How are your samples stored?

Study staff will assign your sample a code number and store it in a freezer. They will not keep your name or other information that could identify you with your sample. They will use the code number to connect your sample to your health information that is stored in a computer database. The computer database is protected with a password. Only study staff will know the password.

Which researchers can use your samples and what information about you can they have?

Your samples will be made available to researchers at MGH and other MGB institutions, as well as non-MGB academic institutions. Occasionally, your samples may be shared with for-profit companies that are working with MGH or other MGB researchers on a specific research project. Your samples will not be sold to anyone for profit. We will usually provide samples with limited information that does not directly identify you.

- As described above, all of the samples being stored are labeled with a code number that connects the sample to medical information related to the sample. The key to the code that links the samples and information to a specific individual will only be available to the study staff, and will be securely stored.
- Researchers at MGB institutions, whose studies have been approved by the hospital ethics board, may be allowed to review your medical record to collect more health information about you. The ethics board is a group that independently reviews and watches over all research studies involving people. The board follows state and federal laws and codes of ethics to make sure that the rights and welfare of people taking part in research studies are protected.
- Researchers outside of MGH will not be given the key to the code that links your sample and medical information to your name or other direct identifiers.

For what type of research will my samples be used?

Your samples and information will be used mainly to understand pain disorders. The long-term goals of the research are to learn how to better understand, prevent, diagnose or treat chronic pain. It is not possible to list every research project. Also, we cannot predict all of the research

questions that will be important over the next years. As we learn more, there are new research questions and new types of research related to pain disorders may be done.

We plan to do genetic research on the DNA in your sample. DNA is the material that makes up your genes. All living things are made of cells. Genes are the part of cells that contain the instructions which tell our bodies how to grow and work, and determine physical characteristics such as hair and eye color. Genes are passed from parent to child.

How long will my samples and information be kept?

There is no scheduled date on which your samples and information in the bank will be destroyed. Your samples may be stored for research until they are "used up."

Can I stop allowing my samples and information to be stored and used for research?

Yes. You have a right to withdraw your permission at any time. If you do, your samples and information will be destroyed. However, it will not be possible to destroy samples and information that have already been given to researchers. If you decide to withdraw your permission, you should contact Dr. Loggia.

What happens if I am injured as a result of taking part in this research study?

We will offer you the care needed to treat any injury that directly results from taking part in this research study. We reserve the right to bill your insurance company or other third parties, if appropriate, for the care you get for the injury. We will try to have these costs paid for, but you may be responsible for some of them. For example, if the care is billed to your insurer, you will be responsible for payment of any deductibles and co-payments required by your insurer.

Injuries sometimes happen in research even when no one is at fault. There are no plans to pay you or give you other compensation for an injury, should one occur. However, you are not giving up any of your legal rights by signing this form.

If you think you have been injured or have experienced a medical problem as a result of taking part in this research study, tell the person in charge of this study as soon as possible. The researcher's name and phone number are listed in the next section of this consent form.

If I have questions or concerns about this research study, whom can I call?

You can call us with your questions or concerns. Our telephone numbers are listed below. Ask questions as often as you want.

Vitaly Napadow, PhD is the person in charge of this research study. You can call him/her at 617-724-3402 M-F 9-5. For questions regarding PET-MR imaging you can also call Nouchine Hadjikhani, MD, PhD at 617-724-5625 M-F 9-5 and Marco Loggia PhD at 617- 643-7267 with questions about this research study.

If you have questions about the scheduling of appointments or study visits, email MigraineRelief@mgb.org or call the Research Coordinator at 617-952-6481.

If you want to speak with someone **not** directly involved in this research study, please contact the MGB Human Research Committee office. You can call them at 857-282-1900.

You can talk to them about:

- Your rights as a research subject
- Your concerns about the research
- A complaint about the research

Also, if you feel pressured to take part in this research study, or to continue with it, they want to know and can help.

If I take part in this research study, how will you protect my privacy?

Federal law requires Partners to protect the privacy of health information and related information that identifies you. We refer to this information as "identifiable information."

In this study, we may collect identifiable information about you from:

- Past, present, and future medical records
- Research procedures, including research office visits, tests, interviews, and questionnaires

Who may see, use, and share your identifiable information and why:

- MGB researchers and staff involved in this study
- The sponsor(s) of the study, and people or groups it hires to help perform this research or to audit the research
- Other researchers and medical centers that are part of this study
- The MGB ethics board or an ethics board outside MGB that oversees the research
- A group that oversees the data (study information) and safety of this study
- Non-research staff within MGB who need identifiable information to do their jobs, such as for treatment, payment (billing), or hospital operations (such as assessing the quality of care or research)
- People or groups that we hire to do certain work for us, such as data storage companies, accreditors, insurers, and lawyers
- Federal agencies (such as the U.S. Department of Health and Human Services (DHHS) and agencies within DHHS like the Food and Drug Administration, the National Institutes of Health, and the Office for Human Research Protections) state agencies, and foreign government bodies that oversee, evaluate, and audit research, which may include inspection of your records
- Public health and safety authorities, if we learn information that could mean harm to you or others (such as to make required reports about communicable diseases or about child or elder abuse)
- Other researchers within or outside MGB, for use in other research as allowed by law.

Certificate of Confidentiality

A federal Certificate of Confidentiality (Certificate) has been issued for this research to add special protection for information and specimens that may identify you. With a Certificate, unless you give permission (such as in this form) and except as described above, the researchers are not allowed to share your identifiable information or identifiable specimens, including for a court order or subpoena.

Certain information from the research will be put into your medical record and will not be covered by the Certificate. This includes records of medical tests or procedures done at the hospitals and clinics, and information that treating health care providers may need to care for you. Please ask your study doctor if you have any questions about what information will be included in your medical record. Other researchers receiving your identifiable information or specimens are expected to comply with the privacy protections of the Certificate. The Certificate

does not stop you from voluntarily releasing information about yourself or your participation in this study.

Even with these measures to protect your privacy, once your identifiable information is shared outside MGB, we cannot control all the ways that others use or share it and cannot promise that it will remain completely private.

Because research is an ongoing process, we cannot give you an exact date when we will either destroy or stop using or sharing your identifiable information. Your permission to use and share your information does not expire.

The results of this research may be published in a medical book or journal, or used to teach others. However, your name or other identifiable information **will not** be used for these purposes without your specific permission.

Your Privacy Rights

You have the right **not** to sign this form that allows us to use and share your identifiable information for research; however, if you don't sign it, you can't take part in this research study.

You have the right to withdraw your permission for us to use or share your identifiable information for this research study. If you want to withdraw your permission, you must notify the person in charge of this research study in writing. Once permission is withdrawn, you cannot continue to take part in the study.

If you withdraw your permission, we will not be able to take back information that has already been used or shared with others, and such information may continue to be used for certain purposes, such as to comply with law or maintain the reliability of the study.

You have the right to see and get a copy of your identifiable information that is used or shared for treatment or for payment. To ask for this information, please contact the person in charge of this research study. You may only get such information after the research is finished.

Research Consent to Receive Unencrypted Text Message Communications

Text messages by mobile/cell phones are a common form of communication. The Migraine Relief research study involves sending you text messages that are relevant to the research study. Texting over mobile/cell phones carries security risks because text messages to mobile/cell phones are not encrypted. This means that information you send or receive by text message

could be intercepted or viewed by an unintended recipient, or by your mobile/cell phone provider or carrier.

Below are some important points about texting in this research study.

- Text messages are not encrypted, and therefore carry security risks. This research study and Mass General Brigham are not responsible for any interception of messages sent through unencrypted text message communications.
- You will be responsible for all fees charged by your carrier's service plan for text messaging. This research study and Mass General Brigham are not responsible for any increased charges, data usage against plan limits or changes to data fees from the research texts.
- Text messages will only be read during regular business hours. Texts sent on nights or weekends will not be read until the following business day.
- Text messaging should not be used in case of an emergency. If you experience a medical emergency, call 911 or go to the nearest hospital emergency department.
- You may decide to not send or receive text messages with staff associated with this research study at any time. You can do this in person or by contacting the Research Coordinator via email or phone.
- Your agreement applies to this research study only. Agreeing to other texts from Mass General Brigham, for example appointment reminders, is a separate process. Opting out of other texts from Mass General Brigham is a separate process as well.
- It is your responsibility to update your mobile/cell phone number with this research study in the event of a change.

I have had the chance to ask questions about texting with staff associated with this research study. I have been informed of the risks and other information covered above and consent to the use of unencrypted text communications associated with this research study.

Do we have your permission to send text messages for scheduling, appointment, or daily diary reminders?

Yes No Initials_____

Informed Consent and Authorization

Statement of Person Giving Informed Consent and Authorization

- I have read this consent form.

- This research study has been explained to me, including risks and possible benefits (if any), other possible treatments or procedures, and other important things about the study.
- I have had the opportunity to ask questions.
- I understand the information given to me.

Study Options

PET-MR with A-Line ☐ PET-MR without A-line ☐ MR only ☐

Do you agree participate in the PET-MR portions of the study?

Yes No Initials_____

If yes, do you agree to have an A-line placed during the PET-MR portions of the study?

Yes No Initials_____

Signature of Subject:

I give my consent to take part in this research study and agree to allow my identifiable information to be used and shared as described above.

_____
Print Name

_____ _____ _____
Subject Date Time

Signature of Study Doctor or Person Obtaining Consent:

Statement of Study Doctor or Person Obtaining Consent

- I have explained the research to the study subject.
- I have answered all questions about this research study to the best of my ability.

_____
Print Name

_____ _____ _____
Study Doctor or Person Obtaining Consent Date Time

Consent Form Version Date: April 22nd, 2024