Consent Form

Study: Vagus Nerve Stimulation: Integration of Behavior and Cardiac Modulation

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Partners HealthCare System
Research Consent Form

Subject Identification

General Template
Version Date: February 2010

Protocol Title: Vagus Nerve Stimulation: Integration of Behavior and Cardiac Modulation

Principal Investigator: Jill Goldstein, PhD

Site Principal Investigator:

Description of Subject Population: Subjects with and without Major Depressive Disorder

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.

Partners HealthCare System is made up of Partners hospitals, health care providers, and researchers. In the rest of this consent form, we refer to the Partners system simply as "Partners."

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.

Why is this research study being done?

The goal of this study is to learn about parts of the brain that control mood and heart rate. We have asked you to take part in this research study because you either have major depressive disorder (MDD) or are being enrolled as a volunteer without MDD.

This research study will use an MRI scan called "functional magnetic resonance imaging" (fMRI). This type of MRI (which use large magnets to take the pictures; there is no radiation exposure) measures brain activity by detecting changes in blood flow. When an area of the brain is in use, blood flow to that region increases. Using the fMRI, we will study the parts of your brain involved in both mood and heart rate.

We will also study whether stimulation to the skin near a branch of the vagus nerve in the outer ear can affect brain activity in these regions, as well as affect your mood and heart rate. This stimulation is called transcutaneous vagus nerve stimulation (tVNS). The vagus nerve runs from your brainstem through your neck to your chest and abdomen.

We will be carefully checking your heart and breathing rate throughout the testing procedures.

Sometimes vagus nerve stimulation is done with an implant requiring a surgical procedure. However, in this study, the vagus nerve stimulation is done by temporarily applying stimulation to your ear. Implanted vagus nerve stimulation is approved by the U. S. Food and Drug Administration (FDA) to treat adults with depression. The non-invasive (non-surgical) method used in this study is not approved by the FDA.

Researchers are studying whether vagus nerve stimulation might also help heart conditions, which are more common in patients with depression. Some people with depression have an abnormal heart rate. Understanding how the brain controls both heart rate and mood may give us insight into these disorders occurring at the same time (depression and heart disease).

About 25 female, right-handed subjects will take part in this research study at Brigham and Women's Hospital (BWH). The first 5 subjects enrolled in the study will not have major depressive disorder (MDD). These non-MDD (test) subjects will do some of the study procedures so that we can make any changes before we enroll subjects with major depression. Subjects with major depression will have a screening and evaluation visit and two MRI testing sessions. The non-MDD test subjects will participate in one MRI session only.

This is a pilot study. Pilot studies are done on a small group of subjects to learn if a larger study would be useful.

How long will I take part in this research study?

It will take you about 2 to 3 weeks to complete this research study. During this time, we will ask you to make 3 study visits (one Screening and Evaluation Visit and two MRI visits) and 4 follow-up evaluations. Non-MDD subjects will not participate in the Screening and Evaluation visit; they will have one study/MRI visit only, to help us finalize our procedures.

What will happen in this research study?

Screening and Evaluation Visit
This visit will last about 1-2 hours. At this visit we will:

- Obtain consent from you, if you choose to participate *(consent from non-MDD subjects will be*

obtained at the MRI appointment).

- Interview you about your past and current mental health.
    - Psychiatric history
    - Hamilton Depression Rating Scale
- Ask you to not take over-the-counter medications for 24 hours before testing sessions to decrease the effect of such medicines on the brain.
- If you are a female who can become pregnant, we will ask you for a urine sample to test for pregnancy. Pregnant and breast feeding women cannot be in the study. *(non-MDD women will be tested for pregnancy at the MRI appointment).*

Visits 1 and 2:
Study Visits 1 and 2 are identical except the stimulation locations on the ear will be different. During these visits, you will have functional magnetic resonance imaging (fMRI), tVNS, and an electrocardiogram.

At these visits, we will:

- Draw blood. Blood will be drawn from you if you are in good health. We will draw one sample [approximately 5 teaspoons (26 ml)] at the beginning of your visit and a second sample after the MRI scan [approximately 3 teaspoons (13 mL)] to measure your hormone and inflammatory markers levels. The results of the blood tests are not clinically relevant to individual persons; therefore, we will not return results to you. However, when the study analyses are complete, we will make study results available to you, if desired (although individuals are not identified in these analyses).

- Collect Saliva. We would like to collect a sample of saliva (15 ml saliva tube) to examine cortisol levels. Collection will take place the evening before the scan (11pm), prior to the scan, and 60 minutes following the picture task. The samples will have no personal identifying information and will be placed in a storage bank in secure buildings in the Boston medical area that have limited access. They will be used only for research that is carefully reviewed and approved both by this study and the Institutional Review Board We will use cortisol levels to evaluate the state of the hypothalamic-pituitary-adrenal (HPA)-axis in depressed subjects

- Ask you to complete some questionnaires about your mood
    - Beck Depression Inventory-II
    - Spielberger State-Trait Anxiety Interview
    - Hamilton Depression Rating Scale
    - Visual Analog Scale

- Prepare you for physiological monitoring and tVNS.
    - An electrocardiogram (ECG) will be performed to check your heart rate. We will place several small, sticky pads on your chest. Each pad has a wire attached. The wires connect to a machine that makes a recording of your heart rhythm. This painless test will continue throughout the fMRI.
    - Breathing rate will be measured using a belt attached around your chest. The belt has a wire attached that connects to a machine that makes a recording of your respiration.
    - The tVNS will include our attaching MRI safe electrodes to your left ear after your ear is cleaned with alcohol. The strength of stimulation will be determined by what you feel before we start scanning. We will ask you if you are comfortable as we adjust the stimulation. We use a level of stimulation that is barely detectable to you.

We will next take you to the MRI room. The MRI scanner uses strong magnetic fields and radio waves to take pictures of your brain. Since MRI uses a large magnet, people who have certain metal implants cannot have this scan. Also, we will ask you to remove all metal items before the scan (for example keys, chains, jewelry, watches, belt buckles, retainers, medication patches, hairpins, coins and credit cards).

The MRI scanner is a large machine shaped like a tube. You will lay on your back on a narrow padded table and will be moved into the MRI tunnel. The tunnel is only a little larger than your body. You will be asked to lay still during the scan. The scanning session, including the breaks, will take about 90 minutes.

You will not feel anything, but you will hear loud noises like knocking or banging. This is the normal noise that the machine makes. We will give you earplugs and headphones to wear to prevent discomfort and any unwanted effects on your hearing.

The fMRI uses the same machine as the standard MRI. During the scan, we will ask you to do a task where you look at a series of pictures. Each time you see a new picture, you will press a button. This task takes about 20 minutes with breaks.

Then you will have tVNS (as explained above) stimulation for 30 minutes.

Afterwards, we will ask you to repeat the picture task. Finally, when you are out of the scanner, you will repeat filling out the mood questionnaires.

We will also take images of your brain that looks at your brain structure (how your brain is formed). We will ask you to lie still during this time, about 6 minutes.

You may stop the fMRI procedure at any time. You will be able to speak to the MRI technician, and the MRI technician will be able to speak to you.

Rarely, we need to repeat some portion of the MRI scan due to quality of information. If this happens, we may ask you to come in to repeat just that part of the MRI session.

You will have a total of 2 fMRI scans during this research study. (Non-MDD test subjects will have only 1).

Post-Scan follow ups:
After each fMRI scan we will follow up with you 1 day and 7 days after. One day after each imaging visit we will ask you to complete a visual analog scale online. This will only take 5 to 10 minutes of your time. In addition, we will ask you to complete some questionnaires about your mood seven days after each imaging visit (Beck Depression Inventory-II, Spielberger State-Trait Anxiety Interview, Hamilton Depression Rating Scale, and Visual Analog Scale). Each one of these follow-up evaluation will take approximately 30 min. The follow up 7 days after the Imaging Visit #1, will be conducted in person at Imaging Visit #2. The second follow up, 7 days after Study Visit #2 will be conducted by phone

After the 2nd 7 day follow up, you will be finished with the study.

If your symptoms of depression worsen or you feel suicidal during any procedure, please tell the technician and the on call psychiatrist will come speak with you.

If at any time after the initial evaluation and between scans, your symptoms of depression worsen, please call our coordinator who can give you treatment referrals between 9 am and 5 pm.

If you cannot wait for a return call, business hours, or feel suicidal, please go to your nearest emergency room or call 911.

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

Magnetic Resonance Imaging (MRI) and Functional Magnetic Resonance Imaging (fMRI):

While there have been no reports of any harmful long-term effects caused by the magnets used in this study or magnets of even higher strength, the long-term effects of being placed in a magnet of this strength are unknown.

Also, although there are no known risks associated with pregnancy, we will not scan someone who is pregnant.

Some people have reported sensations during MRI scans with this magnet, such as "tingling" or "twitching" (or, very rarely, a painful sensation), which are caused by changes in the magnetic field that can temporarily stimulate nerves in your body. With any MRI scan, on occasion, some people experience nervousness or discomfort due to the scanner's small space and the need to lie still. If you have claustrophobia (fear or severe discomfort about being in enclosed spaces), it is very important that you tell the study doctor or study staff about this before you sign this consent form.

Except for pacemakers, some types of metal implants, and medication patches, we are not aware of any other possible dangerous interactions or hazards associated with the MRI scan.

If you experience any discomfort and wish to stop the scan, you can tell the MRI technician, and he or she will stop the scan immediately. In our experience, no one has had sensations from the MRI that did not stop when the scanning stopped.

There are no additional risks associated with repeated MRI sessions, should one be necessary.

Blood draw

You may feel slight discomfort when we insert the needle and draw blood through a vein. Very rarely, the vein may become sore and red. In addition, a temporary, harmless bruise may develop. Although rare, some people faint when blood is drawn. In rare cases, you can get an infection where the blood was drawn. The infection can usually be treated with antibiotics.

Saliva Collection

At this time, there are no known risks for the saliva collection.

Picture presentation

Some people may find that the pictures viewed during the fMRI scanning bring up strong emotions. You can stop the scan at any time if you are uncomfortable.

ECG
We use special ECG electrodes for the MRI scanner so there is no added risk to you. There may be skin irritation from the gel under the electrode during the scan. You can let us know and we can fix the electrodes or you can stop the test.

Breathing rate
The system used for monitoring breathing rate is a commonly used device. It is safe, non-invasive (no surgical procedures involved) and will cause little or no discomfort.

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 scanning and remove the electrodes.

The electrodes that are placed on your ear and attached to the stimulator are covered in silicone and can be used in a scanner. Therefore there is no added risk to you.

Information about possible fMRI findings

In this study, we are doing the MRI scan to answer research questions, not to give you medical care. This MRI scan is not the same as one that your own doctor would order for medical care (a clinical MRI scan). It might or might not show problems that would be found on a clinical MRI scan.

A neuroradiologist (doctor who reviews brain scans) will review all scans and if a medical problem is detected, she/he will contact the principal investigator and let her know. At this time, we will ask your permission to contact your physician. We will send the report and the scan to your physician for proper clinical follow-up with you because the scans that we acquire are only for research purposes and not all of the study staff is trained to find medical problems on brain scans. No information generated in this study will become part of a hospital record on a routine basis.

However, if the study detects a problem on your MRI scan, then this information may become part of your hospital record. If the neuroradiologist thinks that you might have a medical problem and further medical testing shows that there is no problem, then we may have caused you to worry about your health.

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

This study is only for the purpose of research and there will be no benefit to you. The information learned from this study may aid our understanding of how the brain works. This knowledge may help us in future research and in the treatment of neurological and psychiatric diseases affecting mood and heart rate.

Can I still get medical care within Partners 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 Partners 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.

It is possible that we will have to ask you to drop out before you finish the study. 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?

Screening and Evaluation Visit:
You will be paid $25 for the Screening and Evaluation Visit.

fMRI, tVNS, ECG/EKG

Participants with MDD will be paid $150 for participation in each scanning day.

Post-Scan Follow ups

Participants will be paid $25 for the follow up phone call after Study Visit #2.

- We will send you payment in check form. Payment will be sent to you within a few weeks of your last visit.

- If you do not complete the entire study, you will be paid for the parts of the study that you did complete.
- If you only complete one visit, you will still be paid $150 for that visit. If you do not complete the entire visit, you will be paid $15 per hour for the time you participated.

Test (non-MDD) participants will be paid $50 for the scanning session.

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

Study funds will pay for study visits and for tests and procedures done only for research.

Although study funds will pay for certain study-related items and services (for example fMRI, tVNS, ECG), we may bill your health insurer for, among other things, routine items and services you would have received even if you did not take part in the research. You will be responsible for payment of any deductibles and co-payments required by your insurer for this routine care or other billed care. If you have any questions about costs to you that may result from taking part in the research, please speak with the study doctors and study staff. If necessary, we will arrange for you to speak with someone in Patient Financial Services about these costs.

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.

Jill Goldstein, PhD is the person in charge of this research study. You can call her at (617) 525-7517, Monday – Friday, 9 am to 5 pm with questions about this research study.

If you have questions about the scheduling of appointments or study visits, call Dr. Goldstein at 617-525-7517 or her research assistant at 617-525-9666.

If you want to speak with someone **not** directly involved in this research study, please contact the Partners 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?

During this research, identifiable information about your health will be collected. In the rest of this section, we refer to this information simply as "health information." In general, under federal law, health information is private. However, there are exceptions to this rule, and you should know who may be able to see, use, and share your health information for research and why they may need to do so.

In this study, we may collect health 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 health information and why they may need to do so:

- Partners research staff involved in this study

- The sponsor(s) of this study, and the people or groups it hires to help perform this research
- Other researchers and medical centers that are part of this study and their ethics boards
- A group that oversees the data (study information) and safety of this research
- Non-research staff within Partners who need this information to do their jobs (such as for treatment, payment (billing), or health care operations)
- The Partners ethics board that oversees the research and the Partners research quality improvement programs.
- People from organizations that provide independent accreditation and oversight of hospitals and research
- People or groups that we hire to do work for us, such as data storage companies, insurers, and lawyers
- Federal and state agencies (such as the Food and Drug Administration, the Department of Health and Human Services, the National Institutes of Health, and other US or foreign government bodies that oversee or review research)
- Public health and safety authorities (for example, if we learn information that could mean harm to you or others, we may need to report this, as required by law)
- Other:

Some people or groups who get your health information might not have to follow the same privacy rules that we follow. We share your health information only when we must, and we ask anyone who receives it from us to protect your privacy. However, once your information is shared outside Partners, we cannot promise that it will remain 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 health information.

The results of this research study may be published in a medical book or journal, or used to teach others. However, your name or other identifying 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 health 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 health 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.

You have the right to see and get a copy of your health 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.

Informed Consent and Authorization

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.

Study Doctor or Person Obtaining Consent _____ Date/Time _____

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.

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.

Subject _____ Date/Time _____

Consent Form Version: 07/11/2017