Protocol Title: Neuromodulation of lidocaine and capsaicin cream effects on pain experience

Principal Investigator: Jian Kong

Site Principal Investigator:

Description of Subject Population: Healthy adults 21-50

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 aim of this study is to use a brain stimulation tool called transcranial direct current stimulation (tDCS) to investigate the analgesic (reducing sensitivity to pain) effects of lidocaine cream and the hyperalgesic (increasing sensitivity to pain) effects of capsaicin cream using a neutral cream as a control. tDCS stimulation has been shown to temporarily influence the way the stimulated part of the brain functions. With this method, we can study the involvement of specific parts of your brain in the working of the brain as a whole. tDCS is not approved by the U.S. Food and Drug Administration (FDA). This means that tDCS can only be used in research studies. The heat pain device used in this study, the Medoc PATHWAY thermode, is approved by the U.S. Food and Drug Administration (FDA) for evaluating the functionality of human pain

reception and transmission of sensory pathways.

We are asking you to take part because you are a healthy volunteer. A total of up to 90 subjects will be enrolled in this study at Massachusetts General Hospital Charlestown Navy Yard campus. Funding from the National Institute of Health (NIH) is paying for this research to be done.

In some research studies, the investigators cannot tell you exactly what the study is about before you participate in the study. We will describe the tasks in the study in a general way, but we can't explain the real purpose of the study until after you complete these tasks. When you are done, we will explain why we are doing this study, what we are looking at, and any other information you should know about this study. You will also be able to ask any questions you might have about the study's purpose and the tasks you did. Though we may not be able to explain the real purpose of the study until after you complete the tasks, there are no additional risks to those that have been described in this consent form

How long will I take part in this research study?

The study consists of 5 separate sessions, which will take up to four weeks to complete. During this time we will ask you to make 5 visits to the Charlestown Navy Yard Campus of MGH. You must be available to come to the research area at the Charlestown Navy Yard on 5 separate days with each session.

What will happen in this research study?

There are five sessions: Sessions 1 and 2 will be separated by 2-5 days, sessions 2 and 3 will be separated by 1-5 days, then sessions 3, 4, and 5 will be applied on three consecutive days.

You will be in one of three groups: tDCS enhancement, tDCS inhibition, or sham tDCS. We will assign you by chance (like a coin toss) to:

1) tDCS enhancement: In this group, the tDCS stimulates the areas of the brain being examined in this study to increase their activity.

2) tDCS inhibition: In this group, the tDCS inhibits the areas of the brain being examined in this study to decrease their activity.

3) sham tDCS: sham tDCS does not provide real stimulation. Sham will be used to determine if the results of this study are due to the tDCS or other reasons.

You and the study doctor cannot choose your study group. You will have a 1 in 3 chance of being assigned to any of the three groups.

tCDS safely applies a weak electrical current to your scalp using two sponge electrodes that look like flat circular pads. The pads will be held in place on your head with a neoprene cap. The pads will be attached to a generator that will send a weak stimulus to your scalp. This current influences the way that your brain cells work. When the stimulus starts, you might feel a tingling sensation underneath the electrode pads. That sensation is not painful and goes away in seconds.

Session 1 (~1 hour) is a training, familiarity, and calibration session. You will be trained to use a pain rating scale, the Gracely Scale, to describe your experience with an increasing heat stimulus sequence (starting from 38 degrees C). The heat pain stimulator will be attached to your arm using probes by a trained member of the study staff. You will rate three selected temperatures so that we can calibrate your response to the different levels of pain stimulus. You will also be asked to complete questionnaires. During this visit you may be administered a urine drug test to check for substance use. You cannot have ingested alcohol within 48 hours prior to the experiment. Additionally, you cannot use narcotics or other-drugs of abuse.

Session 2 (~1 hour) is a behavioral test session. We will first draw a 3x3 grid on your right forearm to mark nine spaces for heat pain stimulus. There will be three different types of creams used in the study: a neutral control cream, lidocaine (to reduce pain sensitivity), and capsaicin (used to enhance pain sensitivity). The creams will then be applied with each cream spread onto a unique set of 3 adjacent squares. The row placement of the neutral control cream, lidocaine and capsaicin will be randomly determined. The creams will need about 20 minutes to take effect, after which tDCS will be applied for 20 minutes.

To test the hyperalgesic effect of capsaicin and the analgesic effect of the lidocaine, 6 identical pain stimuli will be applied to each of the nine spots. You will be asked to fill out a scale of expectation for relief.

Session 3 (~1.5 hours) is the first fMRI scanning session. We will apply tDCS for 20 minutes. Immediately before and after tDCS, resting state fMRI data will be collected.

We will take detailed pictures of your brain using an MRI (magnetic resonance imaging) scan. An MRI uses a strong magnet and radio waves to take these pictures. Functional magnetic resonsance imaging (fMRI) examines your brain activity during the scan by measuring your blood flow with a magnetic field. Since MRI uses a large magnet, people who have certain metal implants cannot have this scan. You will be asked to remove all metal items before the scan.

The MRI scanner is a large machine shaped like a tube. You will lie on a narrow table and will

be moved into the MRI tunnel. The tunnel is only a little larger than your body. You will be asked to lie still during the scan. The scan will take about 90 minutes.

The MRI makes loud banging noises as it takes pictures. We will give you earphones to reduce the noise. You will be able to hear and speak to the research staff at all times during the scan. We can stop the scan at any time, if needed.

Session 4 (~30 minutes) is a repeated tDCS session with no fMRI scan involved.

Session 5 (~2 hours) is a combined fMRI and tDCS test session. As in Session 3, you will be placed in the fMRI scanner with three different creams administered to each row of squares, with the lidocaine and capsaicin cream administered to the same rows as determined in Session 2. Then, tDCS will be applied based on your randomization to the tDCS enhancement group, tDCS inhibition group, or sham tDCS group. The resting state fMRI data will be collected before and after tDCS. After that, the pain stimulus level we obtained during your earlier Session will be applied during the fMRI scan to only one column on your arm. You will complete the same scale and questionnaire as in the previous sessions. After that, we will administer the same moderate stimulus to all remaining regions on your arm with all 3 creams. At the end of the experiment, you will be debriefed by a licensed physician or the Principal Investigator about the purpose of the study.

In this study, we will also explore the role of genetic factors in pain processing. We will use a DNA Self-Collection Kit (Saliva) (www.dnagenotek.com) to collect your genetic information. We will ask you to spit into a provided saliva collection tube with a funnel until the saliva reaches the marked fill line. You will close the funnel lid, then carefully unscrew the funnel from the top of the tube. The cap must be screwed on the tube tightly before shaking the capped tube for 5 seconds to mix the tube's contents.

FUTURE CONTACT AND SHARING YOUR STUDY INFORMATION

1) We may wish to collect more information from you in the future or for other studies. Is it okay to contact you for additional information or for other studies in the future? Please initial below

____YES, it is OK to contact me again
____ NO, don't contact me again

2) We may choose to share your data with investigators not associated with this project for research on how people experience and process pain sensations. We will send your study data to researchers working with us at MGH. We will label all your study data with a code number instead of your name. The key to the code connects your name to your study data. We will keep the key to the code here at Partners. No one outside Partners will know which

information is yours

Please let us know your decision about sharing your research data for related research. Please initial one of the choices below:

_____ Yes, it's ok for others to use my data for related research.
_____ No, don't share my data with others for related research.

Study Information Included in Your Electronic Medical Record

Information about your taking part in this study won't be placed in your medical records, nor will the results of the research.

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

Transcranial Direct Current Stimulation (tDCS)
tDCS is a safe and painless procedure for healthy people. However, it is not safe for people who have pacemakers, ear implants, shrapnel injuries, or other types of metal or electric devices in their body. Such persons will not be allowed to participate in the study. You must tell your doctor and the investigator about any operations you have had and any metal you may have in your body, so it can be decided if it is safe for you to proceed with the stimulation.

- tDCS has the potential to cause redness of the skin around the area of the electrode pads. Such reddening has been found to go away quickly after the stimulation ends.

- There is a tingling sensation under the electrode pads when the stimulation begins. This sensation is not usually considered painful, but some people find it uncomfortable.

Lidocaine
The local side effects of lidocaine on the skin at the site of application may include blisters, bruising, burning feeling, change in skin color, dermatitis, swelling, removal of skin cells from the top of skin (exfoliation), irritation, skin rash, tiny red or purple spots on the skin, itching, and strange sensations. Signs of an allergic reaction to the drug include tightening of muscles in the lung (bronchospasm), difficult or painful breathing, spasm of the muscles in the vocal cords (laryngospasm), shock, hives, swelling, heightened sensitivity, itch, and skin rash.

Capsaicin
The local side effects of capsaicin may include transient stinging, burning, pain, accumulation of fluid under the skin (edema), swelling, bumps (papules), inflammation (dermatitis), bruising,

hives (urticarial), inflammation, removal of skin cells from the top of skin (exfoliation), redness (erythema), increased sensitivity to pain (hyperalgesia), tingling, prickling, numbness (paresthesia), increased sensitivity to sensations (hyperesthesia), decreased sensitivity to sensations (anesthesia), itching (pruritus), dryness, and abnormal skin color at the application site. Other side effects include headache, burning sensation, peripheral sensory neuropathy, dizziness, abnormal taste (dysgeusia), nausea, vomiting, transient hypertension, cough and throat irritation, cold symptoms (nasopharyngitis), inflammation of the airways of the lungs (bronchitis), and inflammation of the sinuses (sinusitis). The side effects of both lidocaine and capsaicin are uncommon.

Heating Device
There is a small chance that the application of heat pain may cause a burn. However, the highest temperatures that will be used are below that associated with damage to the skin.

fMRI Scan

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.

The MRI scan being done is designed to answer research questions, not examine your brain medically. This MRI scan is not a substitute for one a doctor would order. It may not show problems that would be picked up by a medical MRI scan. However, if we believe that we have found a medical problem in your MRI scan, we will ask a doctor who is trained in reading MRI scans, a radiologist, to help us review the scan. If the radiologist thinks that there may be an abnormality in your MRI scan, we will contact you and will help you get medical follow-up for the problem. If you have a primary care doctor, we can contact your doctor, with your permission, and help him or her get the right follow-up for you. No information generated in this study will become part of a routine hospital record. However, if the study detects an abnormality in your MRI scan, then this information may become part of the MGH hospital record. It is possible that you could be unnecessarily worried if a problem were suspected, but not actually found.

Medical Information

There is a small risk that your confidential medical information could be revealed or discovered by mistake (due to human error). Information about your taking part in this study won't be placed in your medical records, nor will the results of the research. In addition, your information will be coded and the key to the code kept in a separate, locked file. We won't release or publish any information in a way that will identify a specific person.

Questionnaires
You will be asked to fill out a set of psychological questionnaires. If you feel uncomfortable, you can choose not to answer some questions. Drs Dougherty, Gollub, and Camprodon, board-certified psychiatrists, will be available to answer any questions you may have or to consult with you in the unlikely event that evidence of psychological disorder is found.

Genetic Testing
Genetic information that results from this study does not have medical or treatment importance at this time. However, there is a risk that information about taking part in a genetic study may influence insurance companies and/or employers regarding your health. To further safeguard your privacy, genetic information obtained in this study will not be placed in your medical record. Taking part in a genetic study may also have a negative impact on family or other relationships. If you do not share information about taking part in this study, you will reduce this risk.

Concomitant Medications
You may be asked to provide a sample for a urine drug screening to ensure that you are not using any drugs that could interfere with the results of this study. You may not consume alcohol within 48 hours of study visits and may not use narcotics or other drugs of abuse. You will not be required to take any drugs for this study.

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

This study will not have any direct benefit to you. The information we learn from this study may help others in the future if this new information obtained will help to explain the pain reducing effect of lidocaine or pain enhancing effects of capsaicin.

What other treatments or procedures are available for my condition?

Your alternative is not to take part in this research study. Taking part in this study is completely voluntary. You are free to stop taking part at any time. It will not affect any medical care you may receive.

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.

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?

Subjects will be paid by check at the completion of the study for their participation. You will receive $50 for Session 1, $60 for Session 2, $80 for Session 3, $60 for Session 4, $100 for Session 5, and $100 as a bonus if you complete the entire study. Total payment is up to $450 for completion of the entire study. You will receive a free parking voucher for each visit you drive to if necessary.

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

We will not bill you or your insurance company for any part of this study, as all scans and study supplies are paid for through the study fund.

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.

Jian Kong, MD, MPH is the person in charge of this research study. You can call him at 617-962-0978, or M-F 9am-5pm at (617) 726-7893. You can also call Georgia Wilson at (617) 726-5004 M-F 9am-5pm with questions about this research study.

If you have questions about the scheduling of appointments or study visits, call Georgia Wilson at (617) 726-5004.

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 and might use or share your health information without your permission in ways that are not described in this form. For example, we understand that the

sponsor of this study may use your health information to perform additional research on various products or conditions, to obtain regulatory approval of its products, to propose new products, and to oversee and improve its products' performance. We share your health information only when we must, and we ask anyone who receives it from us to take measures to protect your privacy. The sponsor has agreed that it will not contact you without your permission and will not use or share your information for any mailing or marketing list. However, once your information is shared outside Partners, we cannot control all the ways that others use or share it and 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 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 (optional)

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.

Study Doctor or Person Obtaining Consent	Date	Time (optional)

Consent Form Version: 6/25/18