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After reading and discussing the information in this consent form you should know:

- Why this research study is being done;
- What will happen during the study;
- Any possible benefits to you;
- The possible risks to you;
- Other options you could choose instead of being in this study;
- How your personal health information will be treated during the study and after the study is over;
- Whether being in this study could involve any cost to you; and
- What to do if you have problems or questions about this study.

Please read this consent form carefully.

RESEARCH SUBJECT INFORMATION AND CONSENT FORM

TITLE: Frontal stimulation to modulate threat sensitivity in anxious depression

PROTOCOL NO.: 2021-005
WCG IRB Protocol #20210326

SPONSOR: NIGMS

INVESTIGATOR: Maria Ironside, DPhil
6655 South Yale Ave
Tulsa, Oklahoma 74136
United States

SITE(S): Laureate Institute for Brain Research
6655 South Yale Ave
Tulsa, Oklahoma 74136
United States

STUDY-RELATED PHONE NUMBER(S): Tate Poplin
Cell: 918-995-0064

Maria Ironside, DPhil
(918) 502-5169
Cell: 617-417-5065
918-481-4000 (24 hours)

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This consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand. You may have an unsigned copy of this consent form to think about or discuss with family or friends before making your decision.

This is a research study. Research studies involve only individuals who choose to participate. Please take your time to make your decision. Discuss this with your family and friends.

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.

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RESEARCH CONSENT SUMMARY

You are being asked for your consent to take part in a research study. This document provides a concise summary of this research. It describes the key information that we believe most people need to decide whether to take part in this research. Later sections of this document provide all relevant details.

What should I know about this research?

- Someone will explain this research to you.
- This form sums up that explanation.
- Taking part in this research is voluntary. Whether you take part is up to you.
- You can choose not to take part. There will be no penalty or loss of benefits to which you are otherwise entitled.
- You can agree to take part and later change your mind. There will be no penalty or loss of benefits to which you are otherwise entitled.
- If you don't understand, ask questions.
- Ask all the questions you want before you decide to take part.

How long will I be in this research?

We expect that your taking part in this research will last 7 hours over 1-4 weeks.

Why is this research being done?

The purpose of this research is to better understand how frontal stimulation with transcranial direct current stimulation (tDCS) can modulate the brain's activity during various tasks. We hope that the results of this study will help us to understand how to use tDCS to improve treatment outcomes for depression and anxiety.

What happens to me if I agree to take part in this research?

If you decide to take part in this research study, the general procedures include mood questionnaires and interviews, one 30 minute session of tDCS, a 90 minute MRI scan, some behavioral tasks, some of which involve mild electric shocks whilst measuring eye blinks, wearing an actimetry sensor (fitbit) device for 24 hours and a blood draw.

Could being in this research hurt me?

The most important risks or discomforts that you may expect from taking part in this research include tingling under the tDCS electrodes, skin redness and headaches, discomfort from being confined in a small space in the MRI scanner and discomfort from the electric shocks (though these are set by you at a level that you control to be uncomfortable but not painful).

Will being in this research benefit me?

As we are delivering only a single session of tDCS and it is still unproven as a treatment for depression it is not expected that you will personally benefit from this research.

Possible benefits to others include helping in the development of treatments for anxious depression.

What other choices do I have besides taking part in this research?

This study is for research purposes only as the effects of tDCS are still unproven and we are not providing a full course of treatment. Common treatments for depression and anxiety include talking therapy (for example cognitive behavioral therapy or behavioral activation therapy) and medications (for example selective serotonin reuptake inhibitors or bupropion). Please speak to your primary care provider if you are interested in treatment.

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DETAILED RESEARCH CONSENT

Why have you been asked to participate in this study?
You have been asked to participate in this study because you are an individual with major depression and anxiety, English speaking and between 18-65 years old.

Why is this study being done?
The purpose of this research is to better understand how frontal stimulation with transcranial direct current stimulation (tDCS) can modulate the brain's activity during various tasks. TDCS involves placing electrodes on the head (scalp) and passing a very low level of direct current into the brain. During tDCS, electrodes are placed over skull on frontal areas passing a very low level of current. The goal of the study is to determine whether tDCS can modulate the brain's activity during various tasks, which may be important in treatment response. We hope that the results of this study will help us understand if tDCS is effective and how to use tDCS to improve treatment outcomes for depression and anxiety.

What is the status of the devices involved in this study?
This study will use transcranial direct current stimulation (tDCS) with a stimulator made by neuroConn, Starstim, Soterix or similar companies. The transcranial direct current stimulator used in this study is investigational. Investigational means that it has not been approved yet by the U.S. Food and Drug Administration (FDA) for this use.

How many subjects will take part in the study?
A total of 180 subjects with anxious depression will be enrolled and divided in two arms of active and sham stimulation (50% each). You have an equal chance of being in either arm.

What is involved in the study?
All procedures will be carried out at the Laureate Institute for Brain Research.

If you agree to participate in this study as a subject, you will undergo one session of tDCS. You may receive either "real" stimulation or "sham" (not real) stimulation. You will not be told whether you have received a sham or real stimulation procedure. The research staff who are involved in this study will not be informed about the type of stimulation you have received. In case of an emergency, the investigators can find out which stimulation was assigned.

Screening procedures: The screening interview may take about an hour to complete. The screening will entail multiple questionnaires. You have the right to refuse to answer any question that you may not wish to answer. The results of the screening session will be used only for this research and will not become part of your medical record.

You will also be given a brief medical history questionnaire and screening form to complete. Undesirable medical findings may arise during the interview, screening, or MRI scanning. If so, these findings will remain confidential and will be discussed with you by a researcher of this study.

Before the tDCS session, you will be assessed with different questionnaires. Before and after tDCS, you will have a brain imaging performed with MRI. During brain imaging, you will complete computerized tasks that involve pictures. After brain imaging you will carry out a task that involves electric shocks and eyeblink measurements. Finally, you will carry out a task that involves pictures and sounds.

For quality assurance purposes, three photos of the top back and right and left sides of your head might be obtained before and after the stimulation. These photos will be used to check the electrode placement prior and after the tDCS session. Your face will not be in the photo. If you have any identifiable marks on your head, such as a tattoo, birthmark, etc., they will be covered before taking the photo to protect your identity.

You have the right to leave this study at any time for any reason.

TDCS procedures: You will receive a 30 minute session of real or sham tDCS. In real stimulation, up to 2 mAmp of current will be delivered over your scalp using rubber electrodes and paste.

Before we begin to use tDCS, we will see whether you have any broken skin or open wounds in the area where you will be receiving stimulation. If there are, we will not perform stimulation until the skin has been well-healed for 7 days.

During tDCS, you may feel a little tingling/itching. This is normal. The tingling may be very mild and undetectable to some people. In most people, any initial tingling will go away within about a minute.

During the tDCS session, you will lie quietly in the MRI scanner. After stimulation you may notice some redness under the electrode area. This is normal and should resolve within 30-minutes. If it does not resolve, please contact the study staff or investigator.

MRI procedures: Before MRI scanning, you will learn how to complete the cognitive task that will be presented to you in the scanner. Training for the MRI task will last approximately 10 minutes. You will then be placed in the MRI scanner to receive the tDCS and perform the task. The MRI scanner rapidly takes pictures of the brain. The MRI scanner is a metal tube surrounded by a strong magnetic field. During the MRI, you will lie on a table that can slide in and out of the tube. You will be asked to lie still during scanning. Earplugs will be provided to lessen the loud “knocking” sounds that the scanner makes while it is imaging your brain.

First, you will receive a series of short scans that allow us to know where your head is inside the tube. You will then receive a scan lasting 5 to 15 minutes that gives us more detailed pictures of your brain. Finally, you will undergo a series of scans lasting about 60 minutes, during which you will lie at rest, receive tDCS and perform the tasks. During all of these scans, it will be very important to remain still. Your time in the scanner will be about 1.5 hours.

If you are female, a urine pregnancy test will be obtained. An over-the-counter urine pregnancy test will be completed just prior to any MRI scanning. You will not be allowed to participate in the study if the pregnancy test reads positive.

Eyeblink task procedures: After MRI scanning you will complete a task that measures your eyeblinks. Electrodes will be attached below your eye to measure this. During this task you will receive electric shocks which are not dangerous but designed to be uncomfortable. You will decide the intensity of the shocks before the eyeblink task and can stop the task and the shocks at any time.

Behavioral task procedures: After the eyeblink task you will complete a cognitive task with pictures and sounds. You will receive an additional payment (of up to $5) which will depend on your performance in this task.

Blood sample procedures: Finally, after the eyeblink task a trained nurse will take a small amount of blood from a vein in your arm. Blood will be collected using sterile techniques by a person experienced in drawing blood. The blood will be used for the measurement of various immune markers, metabolic panels, and for genetic analysis. The research might include whole genome sequencing (determining the order of DNA building blocks (nucleotides) in your genetic code). For more information, please consult your study doctor.

Wrist actigraphy: You may be asked to wear a small device on your wrist that is about the size of a wristwatch. This device will record your physical activity during the day and sleep quality at night. You will be asked to wear the watch both at night and during the day for the day before until the day after the experimental session.

Follow-up procedures: The day after the experimental session you will return to LIBR to fill out some questionnaires and return the wrist device. One week later we will call you briefly to have a final follow up.

How Long Will You Be in The Study?
This study will have one or two screening sessions (1-2 hours), a tDCS and brain mapping session (4.5 hours), a brief (30-60 min) follow-up session the day after the tDCS visit and a 5 min phone call one week later.

What Are the Risks of The Study?
1. Headaches/itching/paresthesias. Headaches, itching, and paresthesias (burning or prickling sensations that happen without warning) are generally very mild with tDCS and are limited to the actual treatment duration. Since skin nerves get used to the electrical stimulation rather quickly, most people are not aware of the stimulation after about the first 1-minute. More persistent headache can be treated with acetaminophen or ibuprofen.
2. Skin irritation. Skin redness is common with tDCS studies because the electrical stimulation increases local blood flow under the electrodes. This redness should disappear within 30-minutes or less.

3. MRI Risks: There are few risks for the MRI (brain imaging)
    - Physical discomfort: you may feel some discomfort, fatigue, and muscular aches from lying on your back for approximately 90 minutes in the scanner. Minimal discomfort may occur from the fingertip cuff that measures your heart rate.
    - MRI tests are very sensitive and can sometime see something that might need more evaluation. If that happens, you or your insurance company would be responsible for the costs of follow-up testing or care.
    - Metal: the MRI machine produces a constant strong magnetic field, so if you have metal implants or clips within your body they may be influenced by the magnetic field and shift in position. This is a risk if you have a history of: a cardiac pacemaker; metal fragments in your eyes, skin, or body; heart valve replacement; brain clips; venous umbrella; being a sheet-metal worker or welder; aneurysm surgery; intracranial bypass; renal or aortic clips; prosthetic devices such as middle ear, eye, joint, or penile implants; joint replacements; hearing aid; neurostimulator; insulin pump; I.U.D.; shunts/stents; metal mesh/coil implants; metal plate/pin/screws/wires, or any other metal implants; permanent eyeliner or eyebrows. Thus, if you have such implants you must inform us, and you cannot participate in this study. Metal earrings and necklaces also must be removed prior to the study.
    - Hearing: the MRI scanner produces a loud high frequency tone that can cause hearing damage if appropriate hearing protection is not used. Adequate hearing protection in the form of foam ear-plugs and/or headphones will be provided and required. Minimal discomfort may occur from the use of this hearing protection.
    - Claustrophobia: the head holder fits closely around your head, so if you feel anxious in confined spaces you may not want to participate. If you decide to participate, and then at a later time decide to discontinue, just let us know and we will stop the experiment.
    - Dizziness: on occasion individuals undergoing MRI might become dizzy. If you become dizzy while in the magnet, use the intercom to inform the scanner operator; do not leave the scanner gurney table without assistance from the scan operator. We will evaluate your dizziness at the scanning site. We may make recommendations about your dizziness, including recommending that you not leave the scanning center until you are no longer dizzy. In more severe cases of dizziness the investigator might recommend that you no longer continue with the study.
    - Muscle twitching and skin sensations: at times individuals undergoing MRI can experience muscle twitching or skin sensations, such as tingling or pain, that are unrelated to any physical contact. If you experience these sensations, please use the intercom to contact the scanner operator, who will stop the scan. In cases of clear muscle twitching, the research team is likely to recommend that you end participation in the study.
4. Loud Noises. The loud noises are unpleasant but not harmful. They may make you jump at first or make you anxious.
5. Blink Recording. Recording blinks via electrodes is safe, and does not require needles, drugs, or dyes. There is a slight possibility of skin irritation; however, this is rare (less than 1%).

6. Electric shocks. The electric shocks that you will receive are intended to make you anxious. They are not dangerous. We will try to find a level of intensity that is unpleasant, but tolerable and you will be in control of setting this level. If you find the shocks too uncomfortable, you can stop the experiment and withdraw from the study at any time.
7. Some of the pictures and sounds used in the behavioral tasks may be of disturbing material (e.g. dead bodies).
8. **Since this is an investigational instrument for depression and anxiety, the tDCS procedure may involve risks that are currently unforeseeable.**

Procedures are available to stop procedures:
The tDCS procedure can be stopped immediately for any concerns. During the study, please speak freely to the investigators at any time if you become alarmed or scared and want to stop tDCS for any reason.

Are there benefits to taking part in the study?
TDCS is being explored as potential therapy for depression and anxiety. However, since this is a research study, there may be no direct benefit to you from participating. Your participation may help people with depression and anxiety in the future.

What are the costs?
Neither you nor your insurance will be charged for any of the study tests. If you need to be hospitalized voluntarily or involuntarily, Laureate Institute for Brain Research does not intend to provide payment for this. You, or your insurance provider, will be billed for the payment.

Will You Be Paid for Participating in This Study?

Screening/ reassessment session @ LIBR	**TIME**	**PAYMENT**
Consent & Safety Checklists & Questionnaires (extra 1 hour of screening will be necessary if initial screening was greater than 1 month before experimental session)	1-2 hours	$20-$40 ($10 per half hour)
Brain scan & stimulation session @ LIBR		
Orientation, questionnaires and preparation	1.5 hour	$75
Brain mapping	1 hour	$50
Brain stimulation (tDCS)	0.5 hour	$25
Eyeblink task	1 hour	$50
Behavioral task	0.5 hour	$25
Behavioral task additional payment		up to $5
Blood draw		$25
Follow-up session after Stimulation @ LIBR		
Questionnaires	1 hour	$20
Total for completion	6.5/ 7.5 hours	$290/$310 + up to $5

If you do not complete the entire study, your payment will be prorated according to the table above. Your payment can be adjusted according to extra time you are needed to spend on this project based on the standard institutional rates. Any potential need to spend time more than the above table will be reviewed with you ahead of time before signing the consent form.

You will be paid with a ClinCard (similar to a debit card) after each study visit. The compensation on the ClinCard is available for use 24 hours after you return the fitbit device. We will need to obtain certain information from you in order to process the ClinCard. This information will be your name, address, and social security number. This information will only be used for processing your payment and will only be seen by the investigators and the accounting department that processes the payment to you. If you receive $600 or more in subject payments in one year you will receive a 1099 form to file with the IRS. This is to comply with IRS guidelines.

Your specimens (even if identifiers are removed) may be used for commercial profit. You will not share in this commercial profit.

What other options are there?
This study is for research purposes only as the effects of tDCS are still unproven and we are not providing a full course of treatment. Common treatments for depression and anxiety include talking therapy (for example cognitive behavioral therapy or behavioral activation therapy) and medications (for example selective serotonin reuptake inhibitors or bupropion). Please speak to your primary care provider if you are interested in treatment.

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AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

What information may be used and given to others?
The study doctor will get your personal and medical information. For example:

- Past and present medical records
- Research records
- Records about phone calls made as part of this research
- Records about your study visits

To help us protect your privacy, Dr. Ironside has obtained a Confidentiality Certificate from the Department of Health and Human Services (DHHS). The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

What happens to the information collected for this research?
The purpose of this study is research and not clinical treatment or care; thus, results of your individual participation will not be shared with you. We may use, maintain and share the information we collect about you during the research for data analysis and it may be used in future research studies. If we share your information with other researchers it will be de-identified, which means that it will not contain your name or other information that can directly identify you. This research may be similar to this study or completely different. We will not ask for your additional informed consent for these studies. The results of this study may be published in an article or presentation, but we will keep your name and other identifying information confidential.

Who may use and give out information about you?
Investigators at the Laureate Institute for Brain Research frequently collaborate with researchers at other nonprofit research institutions or commercial organizations. The data collected as part of this study, including interviews and medical information, research test results, and blood samples may be shared with these collaborators. Identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject. Any data shared will not include your name or other personally identifiable information. Your permission to use your personal and medical information for this research study will not expire.

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Who might get this information?
Laureate Institute for Brain Research, Inc. is the sponsor of this research. "Sponsor" means any persons or companies that are working for or with the sponsor, or owned by the sponsor.

Your information <u>may</u> be given to:

- The U.S. Food and Drug Administration (FDA),
- Department of Health and Human Services (DHHS) agencies,
- WCG Institutional Review Board (WCG IRB)

Why will this information be used and/or given to others?

- to do the research,
- to study the results, and
- to make sure that the research was done right.

If the results of this study are made public, information that identifies you will not be used. We may publish the results of this research. However, we will keep your name and other identifying information confidential.

What if I decide not to give permission to use and give out my health information?
You will not be able to be in this research study.

May I review or copy my information?
Yes, but only after the research is over.

May I withdraw or revoke (cancel) my permission?
At any time after signing this Authorization, you can change your mind and revoke it.
To revoke this Authorization, you will send a written letter to:

Maria Ironside, DPhil
Laureate Institute for Brain Research
6655 South Yale Avenue
Tulsa, Oklahoma 74136

- If you revoke this Authorization, researchers may only use and disclose the Personally Identifiable Information (PII) already contributed to this research study.
- If you change your mind and revoke the Authorization, you will not be allowed to continue to participate in the study.

Is my health information protected after it has been given to others?
Although we will always try to protect your personal information, there is a risk that your information will be given to others without your permission.

Does my authorization expire?
Unless revoked, your authorization will not expire.

If you have any questions or concerns about your privacy rights, you should contact the LIBR Privacy Officer at 918-502-5155 or via email at privacy@laureateinstitute.org.

What If You Are Injured While Participating in This Study?
In case you get hurt or sick resulting from this study, emergency medical treatment is available. In the event of emergency, you should call 911. Be sure to tell the emergency staff and other healthcare providers of your participation in this study. Contact the investigator of this study, Maria Ironside, DPhil as soon as possible using the contact information at the beginning of this consent. You can call the Investigator if you have questions or concerns. Your health insurance provider may be billed to cover the cost of the medical or emergency services provided. No funds have been set aside by the Laureate Institute for Brain Research to compensate you in the event you are hurt or get sick.

Who Will Provide Funding?
Funding for this research study will be provided by the Laureate Institute for Brain Research.

What Are Your Rights as A Participant?
Taking part in this study is voluntary. You may choose not to participate. Refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled. If you agree to participate and then decide against it, you can withdraw for any reason and leave the study at any time. You may discontinue your participation at any time without penalty or loss of benefits to which you are otherwise entitled.

Your participation in this study may be stopped at any time by the study doctor or the sponsor without your consent for any of the following reasons:

- if it is in your best interest;
- you do not consent to continue in the study after being told of changes in the research that may affect you;
- or for any other reason.

What If There Are New Findings?
We will provide you with any significant new findings developed during the course of the research that may affect your health, welfare or willingness to continue your participation in this study. You may be asked to sign a revised consent form if this occurs.

Whom Should You Call If You have Questions or Problems?
If you have questions, concerns, or complaints about the study or have a research-related injury, contact the investigator, Maria Ironside, DPhil, Laureate Institute for Brain Research at 918-502-5169, 617-417-5065 (cell), 918-481-4000 (24 hours) or for emergencies call 911.

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If you have questions about your rights as a research subject or if you have questions, concerns, or complaints about the research, you may contact:

WCG Institutional Review Board (WCG IRB)
Telephone: 855-818-2289
E-mail: researchquestions@wcgirb.com

WCG IRB is a group of people who perform independent review of research.

WCG IRB will not be able to answer some study-specific questions, such as questions about appointment times. However, you may contact WCG IRB if the research staff cannot be reached or if you wish to talk to someone other than the research staff.

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

Your contact person for this study is: Maria Ironside, DPhil.

She can be reached during business hours by: (918) 502-5169.

If you agree to be in this study, you will be given a signed and dated copy of this consent form.

Signature
I have read the information in this consent form. I have been given an opportunity to ask questions. All my questions about the study and my participation in it have been answered.

I Agree to Participate in This Study
I authorize the use and disclosure of my health information to the parties listed in the authorization section of this consent for the purposes described above.

By signing this consent form, I have not given up any of my legal rights.

Consent Instructions
Consent: Subjects 18 years and older must sign on the subject line below.

_____
PRINTED NAME OF SUBJECT

Consent Signature

_____ _____
SUBJECT SIGNATURE (18 years and older) Date

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I confirm that the research study was thoroughly explained to the subject. I reviewed the consent form with the subject and answered the subject's questions. The subject appeared to have understood the information and was able to answer the following questions correctly:

1. What is the purpose of this study?
2. If you decide to be in the study, what will you be asked to do?
3. What is the possible benefit of participating in this study?
4. What are the possible risks of participating in this study?
5. If you decide not to participate in this study, what options do you have?
6. Will participating in this study cost you anything? If so, what will you have to pay for?
7. Do you have to be in this study?
8. If you decide to be in the study, can you leave the study when you want to?

Printed Name of Person Conducting the Informed Consent Discussion	Position
Signature of Person Conducting the Informed Consent Discussion	Date