STUDY INFORMED CONSENT

Causal Role of Delta-Beta Coupling for Goal-Directed Behavior in Anhedonia

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University of North Carolina at Chapel Hill
Consent to Participate in a Research Study
Adult Participants

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IRB Study # 21-1321
Title of Study: Causal role of delta-beta coupling for goal-directed behavior in anhedonia
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CONCISE SUMMARY

The purpose of this research study is to use a specific type of non-invasive brain stimulation known as transcranial alternating current stimulation (tACS) to determine its effects on brain activity (measured with electroencephalogram, or EEG, a type of non-invasive brain recording) in patients with Major Depressive Disorder (MDD). The device used is investigational and has not been approved by the FDA, though it has been designated as a nonsignificant risk (NSR) device by the FDA. One third of participants will receive tACS and two thirds will receive sham stimulation or an inactive control procedure for comparison use only.

Participation in this study includes up to three appointments, the first one lasting up to 2 hours conducted virtually, the second one lasting up to 3 hours, and the third one lasting up to 1.5 hours. The appointments will be over the course of about 2 weeks. In the first appointments, we will determine your eligibility to participate in the full study. If you qualify, then the second session with stimulation will be completed. The third session involves magnetic resonance imaging (MRI) that may be scheduled afterwards. We estimate the total time needed to complete study participation to be about 6.5 hours.

This study is not designed to benefit participants and there is little chance that you will benefit from being in this research study. There is a small, but unlikely, chance that you may experience a reduction in the severity of symptoms associated with MDD. Transcranial current stimulation (the application of a very weak electric current across your brain) has been used without reports of any serious side-effects.

What are some general things you should know about research studies?
You are being asked to take part in a research study. To join the study is voluntary. You may refuse to join, or you may withdraw your consent to be in the study, for any reason, without penalty.

Research studies are designed to obtain new knowledge. This new information may help people in the future. You may not receive any direct benefit from being in the research study. There also may be risks to being in research studies.

Deciding not to be in the study or leaving the study before it is done will not affect your relationship with the researcher, your health care provider, or the University of North Carolina-Chapel Hill. If you are a patient with an illness, you do not have to be in the research study in order to receive health care.

Details about this study are discussed below. It is important that you understand this information so that you can make an informed choice about being in this research study.

You will be given a copy of this consent form. You should ask the researchers named above, or staff members who may assist them, any questions you have about this study at any time.

What is the purpose of this study?
Healthy brain function includes rhythmic activity that is associated with cognitive functions. There are abnormal changes in this activity in psychiatric disorders. Non-invasive brain stimulation by weak electric currents applied to the scalp has recently emerged as an appealing approach to correct this abnormal activity.

The purpose of this research study is to test a specific type of non-invasive brain stimulation known as transcranial alternating current stimulation (tACS). tACS is the delivery of weak electric current to the scalp in order to modulate brain activity. While tACS has not been FDA-approved, studies such as this one using tACS are commonly determined to be non-significant risk. We intend to compare tACS vs. sham stimulation to determine their effects on brain activity (measured with electroencephalogram, or EEG, a type of non-invasive brain recording) in patients with Major Depressive Disorder (MDD). Sham stimulation is an inactive control procedure that is for comparison use only and will be indistinguishable by the participant from the active treatment.

You are being asked to be in the study because you expressed interest in response to one of our recruitment materials or you met the following eligibility criteria identified through your medical record.

Additionally, you meet the following criteria:
- Ages 18-65 years
- DSM-5 diagnosis of MDD; non-psychotic
- Able to provide informed consent
- Have normal to corrected vision
- Willing to comply with all study procedures and be available for the duration of the study

- Speak and understand English
- Low suicide risk as determined by the Columbia Suicide Severity Rating Scale (C-SSRS), and by the Hamilton Depression Rating Scale (HAM-D).
- Negative pregnancy test for female participants
- PHQ-8 greater than or equal to 8 prior to the first session
- PHQ-9 greater than or equal to 10 at the second session and a diagnosis of major depressive disorder on the MINI

Are there any reasons you should not be in this study?

You should not be in this study if you have/have had any of the following:

- ADHD (currently under treatment)
- Neurological disorders and conditions, including, but not limited to:
    - History of epilepsy
    - Seizures (except childhood febrile seizures)
    - Dementia
    - History of stroke
    - Parkinson's disease
    - Multiple sclerosis
    - Cerebral aneurysm
    - Brain tumors
- Medical or neurological illness or treatment for a medical disorder that could interfere with study participation (e.g., unstable cardiac disease, HIV/AIDS, malignancy, liver or renal impairment)
- Prior brain surgery
- Any brain devices/implants, including cochlear implants and aneurysm clips
- History of current traumatic brain injury
- (For females) Pregnant or breast feeding
- Anything that, in the opinion of the investigator, would place the participant at increased risk or preclude the participant's full compliance with or completion of the study
- DSM-V diagnosis of moderate to severe substance use disorder or alcohol use disorder in the present, or history of severe substance use disorder or alcohol use disorder, or psychotic disorder within the last 12 months
- Not taking medications for ADHD or benzodiazepines as these medications often produce specific EEG activity that may disrupt our interpretation of the findings
- If major depressive disorder is experienced in episode, the participant must currently be within a depressive episode.
- Contraindications for MRI: ferrous metal inside the body, jewelry must be removable, pacemaker or cochlear implant.

How many people will take part in this study?
Approximately 100 people at the University of North Carolina, Chapel Hill will take part in this study.

How long will your part in this study last?
Participation in this study includes three sessions: the first is up to 2 hours, the second is up to 3 hours, and the third is up to 1.5 hours. The first session is used to evaluate eligibility using clinical assessments. If you are not eligible, then your participation will take approximately 2 hours. If you do qualify, then you are invited to complete the second session lasting approximately 3 hours. Finally, a third magnetic resonance imaging (MRI) session is schedule that will last approximately 1.5 hours. For participants that qualify, we estimate the total time needed to complete the study to be approximately 6.5 hours.

What will happen if you take part in the study?

- You will be asked to provide to complete a W-9 with your social security number for payment.
- Women will be provided with a pregnancy test prior to participation.
- On the first session, your eligibility will be determined based on clinical assessments. If you do not qualify, then your participation will be over after the first session (approximately 2 hours).
- If you qualify for the study, then you will complete the second session that will take approximately 3 hours.
- For this session, pads for tACS will be applied to your scalp using a paste.
- Then, an EEG cap will be fitted to your scalp over those pads.
- Next, you will perform a resting-state recording where you are asked to relax with your eyes open and closed.
- Then, you will complete a task. The task is the expenditure of effort for reward task in which you will be asked to press a button with your index or pinky finger in order to receive a chance a reward.
- Next stimulation is delivered during the performance of the task. In the stimulation condition, a very weak electric current, less than the current delivered by a AAA battery, will be passed through your brain. In the sham condition, the electrodes will initially 'charge up' and a brief electric current will be passed into your brain, but then it will cease and no further current will be passed.
- There are three stimulation conditions: two of the stimulation conditions involve a complex electrical waveform designed to mimic naturally occurring brain activity discovered in our previous study. The third stimulation condition is an active placebo. Which of the three stimulation conditions you are assigned to will be randomized and neither yourself nor the researcher will know which stimulation condition you received.
- Afterwards, we will give you a survey to assess your experiences during the stimulation.
- After the second session, we will schedule your third session that involves magnetic resonance imaging (MRI). This session will be scheduled about a week after the first session, and will take about 1.5 hour. During this MRI session, a high-definition image will be acquired of your brain. In addition, you will rest with your eyes-open and

recordings of your brain activity through time will be acquired. Finally, you will perform the effort based task as in the second session while recording your brain activity.

What are the possible benefits from being in this study?
Research is designed to benefit society by gaining new knowledge. The ability to target abnormal brain activity could lead to treatments for symptoms in patients with depression and other psychiatric conditions. This study is not designed to benefit participants and there is little chance you will benefit from being in this research study. There is a however, small chance that you may experience a reduction in the severity of symptoms associated with MDD.

What are the possible risks or discomforts involved from being in this study?
Transcranial current stimulation (the application of a very weak electric current across your brain) has been used without reports of any serious side-effects. Some subjects report a transient mild tingling, burning, or itching underneath the electrodes and headache, but no other side effects have been noted. Importantly, it remains unclear if these mild side effects were caused by the transcranial brain stimulation. The transcranial stimulator used in this was cleared by UNC Hospital Medical Engineering. During the study, we will ask about your comfort, and the study will immediately be stopped if you are experiencing discomfort.

In theory, there is a possibility that application of weak stimulation current could induce a seizure. However, this has never been reported as occurring. In the unlikely event of this occurring, trained medical professionals are on-site to respond.

Some participants may become claustrophobic upon entering the small space of the MRI bore. To reduce psychological distress, participants are informed that they can withdraw consent and stop participation at any time. Participants are monitored throughout the MRI scans and can terminate the scan at any time by squeezing a ball held in the hand, and will be quickly removed from the MRI bore.

Magnetic resonance imaging (MRI) is a non-invasive imaging modality with an outstanding safety profile in the United States. The risk of physical injury from the presence of metallic objects within the body is almost entirely addressed through the use of screening forms, by requiring participants to change into medical gowns, and by using metal detectors at the site of the MRI. Through using a core facility at UNC-CH, the Biomedical Research Imaging Center (BRIC), we ensure that risks are minimized as BRIC technicians independently screen and prepare participants for imaging.

Patients with MDD have an about 20 times higher rate of suicide than average. We have no evidence that tACS will in any way increase this likelihood. No participants in our previous clinical trial who received tACS reported an increase in suicidal ideation from baseline. Regardless, participants with high suicide risk will not be included in this study. If an enrolled participant shows signs of suicide risks that were not apparent during enrollment, a referral to UNC Psychiatry will be made.

As with all research, there is the possibility for a breach of confidentiality. This will be minimized by only identifying your data with a number. The only code linking your identity and that number will be kept in a locked office.

There may be uncommon or previously unknown risks. You should report any problems to the researcher.

What are the risks to a pregnancy or to a nursing child?

If you are a woman and you are planning to get pregnant, you should not be in the study. Urine pregnancy tests will be used with all females who could be pregnant at the first and second session. Pregnancy tests will be provided by the researchers at no charge to participants.

What if we learn about new findings or information during the study?

You will be given any new information gained during the course of the study that might affect your willingness to continue your participation.

The imaging we are using in this research study is not the same quality as imaging that you may have as part of your health care. The images will not be reviewed by a doctor who normally reads such images (such as a radiologist). As a result, you may not be informed of any unexpected findings. The results will not be placed in your medical record. Occasionally the technologist or principal investigator may notice something abnormal on the imaging. If this does occur, the images will be reviewed by a qualified doctor to determine if there is anything of clinical importance. If something is found to be important then you, and/or your primary care provider will be notified. Any further follow up and costs associated with the incidental finding will be your responsibility. There may be benefits to learning such results (such as early detection and treatment of a medical condition), but there are risks as well (such as problems with getting insurance or a job, or feeling worried about a finding for which no treatment is required or appropriate).

Do you wish to be informed in case of clinical/relevant unexpected findings? Please initial in the box below if you do not wish to be notified of clinical/relevant unexpected findings. If you do not initial in the box, you will be notified of any findings.

_____ I do wish to be notified.

_____ I do not wish to be notified.

How will information about you be protected?

Your name will not be recorded on any data collected. Data will only be identified by a code number. A key connecting your name and code number will be kept in a locked cabinet, accessible only by research personnel. All data will be stored and analyzed on password protected computers, also only accessible by research personnel.

Clinical interviews will be recorded with your permission for the sole purpose of reviewing symptoms with other trained researchers to reach a consensus on diagnoses. No personally identifying information will be included in the recordings. Like all other data, they will be

identified by a code number and kept on a password protected computer. Recordings will be deleted upon study completion. Audio recordings may be requested to be turned off at any time.

Check the line that best matches your choice:

_____ OK to record me during the study

_____ Not OK to record me during the study

Participants will not be identified in any report or publication about this study. We may use de-identified data and/or specimens from this study in future research without additional consent.

Although every effort will be made to keep research records private, there may be times when federal or state law requires the disclosure of such records, including personal information. This is very unlikely, but if disclosure is ever required, UNC-Chapel Hill will take steps allowable by law to protect the privacy of personal information. In some cases, your information in this research study could be reviewed by representatives of the University, research sponsors, or government agencies (for example, the FDA) for purposes such as quality control or safety.

What will happen if you are injured by this research?
All research involves a chance that something bad might happen to you. If you are hurt, become sick, or develop a reaction from something that was done as part of this study, the researcher will help you get medical care, but the University of North Carolina at Chapel Hill has not set aside funds to pay you for any such injuries, illnesses or reactions, or for the related medical care. Any costs for medical expenses will be billed to you or your insurance company. You may be responsible for any co-payments and your insurance may not cover the costs of study related injuries.

If you think you have been injured from taking part in this study, call the Principal Investigator at the phone number provided on this consent form. They will let you know what you should do.

By signing this form, you do not give up your right to seek payment or other rights if you are harmed as a result of being in this study.

What if you want to stop before your part in the study is complete?
You can withdraw from this study at any time, without penalty. The investigators also have the right to stop your participation at any time. This could be because you have had an unexpected reaction, or have failed to follow instructions, or because the entire study has been stopped.

If you withdraw or are withdrawn from this study all data collected up until the point of withdrawal will be retained, however no additional information will be collected unless you provide additional written permission for further data collection at the time of your withdrawal.

Will you receive anything for being in this study?
Participants will be paid at the end of the first session, at the end of the second session, and at the

end of the third session. There will be a minimum number of one session and a maximum of 3 sessions. The following payment schedule will be used:

- **First session (virtual):** $30
- **Second session (stimulation):** $50
- **Third session (MRI):** $40

Participants who withdraw will be paid at the end of their last visit. Additionally, parking in the Dogwood Parking Deck will be covered by the study.

You will be receiving a total of $120 for completing all requirements of the study. Any payment provided for participation in this study may be subject to applicable tax withholding obligations. Your name, address, and U.S. taxpayer identification number (SSN or ITIN) are required to process payments and/or to report taxable income to the IRS. You must complete a W-9 (for U.S. persons) or W-8BEN and the Foreign Vendor Withholding Assessment with supporting documents (for non-resident aliens) to receive payment for participation.

U.S. person participants must complete Form W-9 in order to receive payment for participation. If payment by UNC equals or exceeds $600 per calendar year for U.S. persons, UNC will report the amount to the Internal Revenue Service on Form 1099. Nonresident alien participants must complete Form W-8BEN and the Foreign Vendor Withholding Assessment with supporting documents in order to receive payment for participation. Payments to nonresident alien participants may be subject to tax withholding and are generally reported to the Internal Revenue Service on Form 1042-S. This information will not be linked to any of the study data and will only be used for payment purposes.

If you do not provide your SSN or ITIN, or complete the appropriate documentation noted above, we cannot issue you a payment for participation. However, you may still choose to participate in this study.

Will it cost you anything to be in this study?
It will not cost you anything to be in this study.

What if you are a UNC student?
You may choose not to be in the study or to stop being in the study before it is over at any time. This will not affect your class standing or grades at UNC-Chapel Hill. You will not be offered or receive any special consideration if you take part in this research.

What if you are a UNC employee?
Taking part in this research is not a part of your University duties and refusing will not affect your job. You will not be offered or receive any special job-related consideration if you take part in this research.

Who is sponsoring this study?
This research is funded by the Foundation of Hope (the sponsor). This means that the research team is being paid by the sponsor for doing the study. In addition, David Rubinow, a co-

investigator on this study, participates in unpaid activities which are not part of this study for the Foundation of Hope. These activities may include consulting, service on committees or boards, giving speeches, or writing reports.

If you would like more information, please ask the researchers listed in the first page of this form.

What if you have questions about this study?
You have the right to ask, and have answered, any questions you may have about this research. If you have questions about the study (including payments), complaints, concerns, or if a research-related injury occurs, you should contact the researchers listed on the first page of this form.

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

National Institute of Mental Health Data Archive (NDA)
Data from this study will be submitted to the National Institute of Mental Health Data Archive (NDA) at the National Institutes of Health (NIH). NDA is a large database where deidentified study data from many National Institute of Mental Health (NIMH) studies is stored and managed. Deidentified study data means that all personal information about you (such as name, address, birthdate and phone number) is removed and replaced with a code number. Sharing your deidentified study data helps researchers learn new and important things about mental health and substance use more quickly than before.

During and after the study, the study researchers will send deidentified study data about your health and behavior to the NDA. Other researchers across the world can then request your deidentified study data for other research. Every researcher (and institutions to which they belong) who requests your deidentified study data must promise to keep your data safe and promise not to try to learn your identity. Experts at the NIH who know how to keep your data safe will review each request carefully to reduce risks to your privacy. Sharing your study data does have some risks, although these risks are rare. Your study data could be accidentally shared with an unauthorized person who may attempt to learn your identity. The study researchers will make every attempt to protect your identity.

You may not benefit directly from allowing your study data to be shared with NDA. The study data provided to NDA may help researchers around the world learn more about mental health and substance use and how to help others who have problems with mental health and substance use. NIMH will also report to Congress and on its website about the different studies using NDA data. You will not be contacted directly about the study data you contributed to NDA.

You may decide now or later that you do not want your study data to be added to the NDA. You can still participate in this research study even if you decide that you do not want your data to be added to the NDA. If you know now that you do not want your data in the NDA, please tell the study researcher before leaving the clinic today. If you decide any time after today that you do

not want your data to be added to the NDA, call or email the study staff who conducted this study, and they will tell NDA to stop sharing your study data. Once your data is part of the NDA, the study researchers cannot take back the study data that was shared before they were notified that you changed your mind. If you would like more information about NDA, this is available on-line at http://nda.nih.gov.

What if you have questions about your rights as a research participant?
All research on human volunteers is reviewed by a committee that works to protect your rights and welfare. If you have questions or concerns about your rights as a research subject, or if you would like to obtain information or offer input, you may contact the Institutional Review Board at 919-966-3113 or by email to IRB_subjects@unc.edu.

Participant's Agreement:

I have read the information provided above. I have asked all the questions I have at this time. I voluntarily agree to participate in this research study.

Signature of Research Participant	Date
Printed Name of Research Participant	

Signature of Research Team Member Obtaining Consent	Date
Printed Name of Research Team Member Obtaining Consent	