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The University of Arizona

Consent to Participate in Research

Study Title: The Effect of Transcranial Ultrasound on Default Mode Activity and Behavior

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Funder: Open Water Internet Inc.

Summary of the research

This is a consent form for participation in a research study. Your participation in this research study is voluntary. It contains important information about this study and what to expect if you decide to participate. Please consider the information carefully. Feel free to ask questions before making your decision whether to participate.

The purpose of this study is to determine if transcranial ultrasound can alter brain activity and decrease depression symptoms and preservative thinking. We aim to examine how Default Mode Network activity temporarily changes after using a neuromodulation technique called transcranial ultrasound. First, we will go through the consent together. Then, you will be asked to complete some additional screening questions and interviews to ensure you are eligible for the study. Then there will be a series of study procedures that you will complete. First, you will complete baseline MRI scans and surveys. Then, you will complete up to three weeks of ultrasound treatment, the first week coming in five days in a 7-day week. Then, you will complete MRI scans and surveys asking about your mood and behavior. Following this first portion of the study, you may be asked to come in for more ultrasound sessions (up to 3 times a week) for two more weeks depending on how you respond to treatment. After treatment, you will complete more MRI scans and surveys asking about your mood and behavior. During treatment, you will also complete daily surveys.

Finally, we will follow up with a phone call one month, 3 months, and 6 months after the study procedures are completed to ask you questions about your experiences, mood, and behavior after completing treatment.

The entire study will take 6 months to complete. The screening procedures will take about 2 hours total. The MRI scans will take 30 minutes to complete per scan, and the surveys will take 30 minutes to complete per session. The ultrasound treatments will take about 60 minutes per session. The follow-up phone calls will take about an hour per phone call. You will be compensated $50 per MRI scan and $20 per ultrasound treatment.

There are no direct benefits from being involved in this study, but you may experience improvement in mood and behavior symptoms. There are no major risks associated with participating in this study, but you may experience discomfort or boredom associated with answering sensitive questions (e.g., about mental health). If you do not wish to participate, you have that option. You can terminate participation at any point during the study. This study is completely voluntary.

1. Why is this study being done?

When you are left alone to think for yourself, a core set of brain regions becomes activated, called the default mode network (DMN). The purpose of this study is to understand the nature of this network better. We aim to examine how altering DMN activity using non-invasive transcranial ultrasound improves your mood and behavior.

2. How many people will take part in this study?

Up to 50 individuals will complete this portion of the study.

3. What will happen if I take part in this study?

If you agree to participate in this study, after consenting, the following protocol will take place:

Screening procedures:

You will complete a series of clinical assessments to measure your baseline symptoms related to your mood and behavior. If you are not eligible during either of these steps, the study will terminate immediately.

Baseline MRI scan and surveys:

On a separate day, you will come into the lab and be given detailed information about the MRI scanner and what you will be doing during the scans by our MRI technician. We will be taking images and recordings of your brain. You will also complete surveys about how you feel and behave.

Ultrasound intervention week 1:

Every day for 1 week, you will come into the lab and have a small ultrasound transducer placed on the front of your head. We will use your brain image to target the ultrasound beam to the region of the DMN we wish to target, the anterior medio-frontal prefrontal cortex (amPFC); this is called neuronavigation.

You will receive ten minutes of pulsed ultrasound. The ultrasound will either be placed on your head and held by the researcher or attached with a comfortable strap. You will be asked to sit quietly while the ultrasound is turned on. You should not feel anything physically from the ultrasound as the amount of energy is very low.

You will also complete daily surveys about your thoughts, mood, and behaviors.

Post-week 1 MRI and surveys

After 1 week of the ultrasound intervention, you will be asked to come into the lab on a separate day to complete a second MRI. We will perform the same MRI scans that we did at baseline, with the addition of another scan that will identify any physical side-effects of ultrasound as a measure of safety. You will also complete surveys about how you feel and behave to assess symptoms related to your mood and behavior. If we see a significant reduction

in depressive symptoms and related changes in your brain activity, the intervention phase will be complete. If we do not see significant reduction in symptoms and brain activity, you will be asked to proceed with a phase 2 intervention protocol.

Ultrasound intervention weeks 2-3:

If you have not responded significantly to treatment week-1, you will be asked to come in 2-3 days a week for 2 weeks to complete more ultrasound sessions, using the same protocol as week 1.

You will also complete daily, during this 2-3 week period, surveys about your thoughts, mood, and behaviors.

Post-weeks 2 and 3 MRI and surveys

After weeks 2 and 3 of the ultrasound intervention, you will be asked to come into the lab on a separate day to complete a second MRI. We will perform the same MRI scans that we did at post-week1. You will also complete surveys about how you feel and behave to assess symptoms related to your mood and behavior.

1, 3, 6-month follow-up phone calls and surveys

1, 3, and 6 months after you have completed the intervention phase (week 1 or after week 3), you will be asked to complete a series of surveys via online survey assessing your mood and behavior to see if there are any long-lasting benefits related to the intervention.

Debrief

Once all study procedures are complete, you will be given a detailed conversation about the purpose of this study, and what we hope to understand from your participation.

4. How long will I be in the study?

The screening process will take up to 2 hours total, each MRI session (three total) will take 30 minutes each, each tFUS session will be 60 minutes, and surveys will take about 30 minutes to complete per session.

5. Can I stop being in the study?

Your participation is voluntary. You may refuse to participate in this study. If you decide to take part in the study, you may leave the study at any time. Your data will be discarded or shredded if you leave the study at any time. No matter what decision you make, there will be no penalty to you, and you will not lose any of your usual benefits. Your decision will not affect your future relationship with The University of Arizona. If you are a student or employee at the University of Arizona, your decision will not affect your grades or employment status.

6. What risks, side effects or discomforts can I expect from being in the study?

The procedures that we use on you involve minimal risk or discomfort. You may experience discomfort associated with answering sensitive questions (e.g., about mental health). The act of completing assessment materials may cause boredom or frustration.

Regarding ultrasound use on the body, the Food and Drug Administration (FDA) has issued guidelines for safe human ultrasound use, at or below 720 mW/cm^2 in adult humans, for all parts of the body. The ultrasound used on you will be well below these approved intensity levels, and therefore, the risk to you is minimal. Ultrasound imaging has been used for over 50 years and has an excellent safety record. Although ultrasound imaging is generally considered safe when used prudently by an appropriately trained technician, ultrasound energy has the potential to produce short term biological effects on the body. High-intensity thermal ultrasound is used to ablate (damage) the brain and other tissue throughout the body for therapeutic purposes. However, thermal ablation occurs at intensities that are many times the levels we will employ in this protocol (above 100 watts.cm^2). We are using low-intensity, non-thermal ultrasound (in the milliwatts/cm^2 range). Under 720 mW/cm^2, significant tissue heating is unlikely, and such low-intensity ultrasound does not lead to lasting bioeffects. In some cases, low-intensity ultrasound can also produce small pockets of gas in body fluids or tissues (cavitation) in the lungs or other areas of the body that contain gas pockets. Therefore, the lungs are typically avoided. Although the long-term consequences of low-intensity ultrasound on the body are unknown, the likelihood of long-term negative consequences of one exposure is exceedingly small, and therefore the risk to you is minimal.

The ultrasound gel used on the transducer is hypoallergenic but nonetheless could cause a very mild skin reaction in some subjects. This is very unlikely, but in the case that a researcher notices a mild reaction, or a subject complains of irritation, the study will be stopped immediately

The total ultrasound energy we will use on you is below the FDA limit of 720 mW/cm^2. Additionally, in order to reduce the risk further, the ultrasound will be turned on only for extremely short amounts of time (less than one millisecond) and then turned off for several seconds. There will be no more than 130 total pulses. This means the total amount of ultrasound you will receive over ten minutes is less than 130 seconds.

You should not experience sensations or pain with the low-intensity ultrasound we employ. If they do report any negative sensations, you will be given the option to end the study.

There is a risk of shock if the ultrasound device is not plugged into a grounded outlet. Therefore, we will ensure that it is plugged into a grounded plug at all times.

This research MRI scanner operates within FDA guidelines and is considered a “non-significant” risk device. This means the risks associated with this system are minimal so long as appropriate precautions are taken. Significant risks may exist for people with:

- Cardiac pacemakers
- Metal clips (stents) on blood vessels
- Artificial heart valves or aneurys clips
- Artificial arms, hands, legs, heart valves, etc.
- Brain stimulator devices or other neural stimulators

- Implanted drug pumps or defibrillators
- Ear implants
- Eye implants or known metal fragments in eyes
- Exposure to shrapnel or metal filings (e.g., wounded in military combat, sheet metal workers, welders)
- Other metallic surgical hardware in vital areas
- Certain tattoos with metallic ink (please tell us if you have a tattoo) or permanent makeup (eyeliner)
- Certain transdermal (skin) patches such as NicoDerm (for tobacco dependence), Transderm Scop (for motion sickness), or Ortho Evra (birth control)
- IUD
- Insulin pumps,
- drug infusion devices;
- non-removable metal piercings
- Magnetic dental appliances
- Any type of metal implant, plates, or screws
- Prosthetics
- pregnancy

Please let the technologist know if you have any of these items or anything else metallic or magnetic that will not be removed before the MRI scan.

Significant risks can also arise if metallic/magnetic objects and materials are brought into the scanning area with you (e.g., as part of your clothing, in your pockets, around neck). Such items will get pulled into the magnet at great speed and can cause serious injury. You will not be allowed to bring anything with you into the scanning room.

While MRI of a fetus is used clinically, the effects of MRI on the early development of the fetus are unknown. If you are pregnant, you will be removed from the study.

The Siemens MRI scanner that will be used for your scan is approved by the FDA for routine clinical and research studies. This is also true for most of the peripheral components used with the scanner as well as most of the scan types (called sequences) that are performed on the scanner.

The noises that you hear inside the scanner are normal. You will be given ear protection to help muffle the noise. The noise may be annoying, but it is not harmful. The scanner may be uncomfortable if you have trouble laying on your back for long periods of time and you may find the experience unsettling if you are bothered by small spaces.

There are no known side effects of ultrasound on the brain. However, participants have reported slight headaches that may be related to this procedure. If you feel any negative effects, let the researcher know immediately.

The magnetic resonance imaging device is a very strong magnet and poses a risk if you have any metal on your body. Therefore, we will ask you to empty your pockets and take off all metal before going into the magnet. MRIs are considered noninvasive and safe and have no long-term effects.

The technology we use to identify the brain region we will ultrasound poses no risk to you.

Please inform the experimenter if you are experiencing any unexpected increase in negative mood or other symptoms. Importantly, your participation is entirely voluntary, and you may withdraw from the experiment at any time without penalty. It is also possible that feelings of low mood or suicidal thoughts may develop or increase throughout the study. If you feel that you are experiencing increased mood difficulties or suicidal thoughts, please inform the investigator. The investigator will be reviewing baseline surveys and will assess if there is suicidally risks and address accordingly.

7. What benefits can I expect from being in the study?

You will not receive any benefits from taking part in this study other than a potential, temporary improvement in your mental or emotional state. You may perceive an elevation in mood from the ultrasound procedure. There is no medical benefit for participation in this scan. You may request a copy of your scan.

8. What other choices do I have if I do not take part in the study?

The alternative is not to participate in this study.

9. Will my study-related information be kept confidential?

Efforts will be made to keep your study-related information confidential. We will give you a unique ID number, which will go on all your records in our study, and all identifying information (like your name) will not be attached to any of your data, except this consent form. Your data will be stored in Babcock under lock or on a secure computer server in the psychology department.

At the end of the study, the consent form will be stored in Babcock, under lock, for six years. Therefore, all efforts will be made to ensure your data cannot be identified as yours. However, there may be circumstances where this information must be released. For example, personal information regarding your participation in this study may be disclosed if required by state law. Also, your records may be reviewed by the following groups (as applicable to the research):

- Office for Human Research Protections, the FDA, or other federal, state, or international regulatory agencies;
- The University of Arizona Institutional Review Board; *Or*

  The sponsor of the study, if any, may review the research records for monitoring purposes.

The survey data we record will be stored on the Qualtrics Inc. servers. Qualtrics is approved by the University of Arizona for the online survey and has high-level data security servers and protocols. We will back-up survey data to our psychology department sever.

Your de-identified interview, survey, and MRI data will be retained for potential future analysis beyond the aims of this study.

10. Will I hear back on any results that directly impact me?

Your MRI scans are not intended to provide medical benefit to you, and the technologist and/or investigators running your scan are not trained or licensed to clinically review your images. If a technologist and/or investigator notices something they think is unexpected in your images, the investigator may provide de-identified images to a licensed radiologist for further review. In the extremely rare case that this radiologist finds an irregularity, the technologist or investigator will contact you and recommend that you consult your primary care physician. You will be provided copies of your images, but otherwise, this will be on your own time and at your own cost. The University of Arizona and its employees have no funds set aside for the payment of treatment expenses that may arise from you volunteering for an MRI scan.

There may be instances in which an abnormality exists but is not noticed by the technologists or investigators. In addition, there may be instances where you have one or more pre-existing conditions that make it impossible to determine if a scan shows something unexpected. We are not trained to clinically review images, and our data and/or analyses are not intended to treat, diagnose, or replace the expertise of a medical doctor or a medical diagnosis. As such, the University of Arizona and its employees are not responsible for abnormalities that go undetected through participation in these volunteer activities. Please do not rely on our data and/or analyses to reveal abnormalities.

11. What are the costs of taking part in this study?

Aside from your time, there are no costs for taking part in the study.

12. Will I be paid for taking part in this study?

You will receive $50 per MRI session and $20 per treatment day. You will also receive $20 for each follow-up assessment (1, 3, and 6 months after completion of study procedures).

Compensation for participation in a research study is considered taxable income for you. We are required to obtain your name, address, and Social Security number for federal tax reporting purposes. If your compensation for this research study or a combination of research studies is $600 or more in a calendar year (January to December), you will receive an IRS Form 1099 to report on your taxes.

13. What happens if I am injured because I took part in this study?

If you suffer an injury from participating in this study, you should seek treatment. The University of Arizona has no funds set aside for the payment of treatment expenses for this study.

14. What are my rights if I take part in this study?

If you choose to participate in the study, you may discontinue participation at any time without penalty or loss of benefits. By signing this form, you do not give up any personal legal rights you may have as a participant in this study. You will be provided with any new information that develops during the course of the research that may affect your decision whether or not to continue participation in the study. You may refuse to participate in this study without penalty or loss of benefits to which you are otherwise entitled. An Institutional Review Board responsible for human subjects research at The University of Arizona reviewed this research project and found it to be acceptable, according to applicable state and

federal regulations and University policies designed to protect the rights and welfare of participants in research.

15. Will my study-related information be used for future research?

Your de-identified data may be used for future research with colleagues internally at the University of Arizona or other academic researchers for any research purpose. Since your data will be de-identified, we will not require your consent. We will never sell your data or give you data to for-profit institutions or companies.

16. Who can answer my questions about the study?

For questions, concerns, or complaints about the study, you may contact John JB Allen, jallen@email.arizona.edu, 520-621-4992.

For questions about your rights as a participant in this study or to discuss other study-related concerns or complaints with someone who is not part of the research team, you may contact the Human Subjects Protection Program at 520-626-8630 or online at https://research.arizona.edu/compliance/human-subjects-protection-program.

If you are injured as a result of participating in this study or for questions about a study-related injury, you may contact John JB Allen, jallen@email.arizona.edu, 520-621-4992.

Signing the consent form

I have read (or someone has read to me) this form, and I am aware that I am being asked to participate in a research study. I have had the opportunity to ask questions and have had them answered to my satisfaction. I voluntarily agree to participate in this study.

I am not giving up any legal rights by signing this form. I will be given a copy of this form.

Printed name of subject	Signature of subject	Date

Investigator/Research Staff

I have explained the research to the participant or the participant's representative before requesting the signature(s) above. There are no blanks in this document. A copy of this form has been given to the participant or to the participant's representative.

Printed name of person obtaining consent	Signature of person obtaining consent	Date