Title: Closed-Loop Brain Stimulation as a Potential Intervention for Cognitive Decline

NCT number: NCT05907343

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Consent to Participate in Research

Basic Study Information

Title of the Project: Closed-Loop Brain Stimulation as a Potential Intervention for Cognitive Decline
Principal Investigator: José del R. Millán, PhD, UT Austin (Dept. of ECE & Dept. of Neurology)
Funding Source: Texas Alzheimer's Research Care Consortium (TARCC)

Invitation to be Part of a Research Study

You are invited to be part of a research study. This consent form will help you choose whether or not to participate in the study. Feel free to ask if anything is not clear in this consent form.

Important Information about this Research Study

1. Why are we doing this study?
We want to find out if a special type of brain stimulation (called closed-loop TMS) works better than the usual type of stimulation (open-loop TMS) for improving reasoning and memory. We hope this new method can help people focus better and remember things more easily.

2. Who can join?
You can join if you:

- Are between 60 and 90 years old
- Are in good general health
- Have normal vision, or wear glasses or contacts to see well
- Have finished elementary school or can understand middle school instructions
- Have not been diagnosed with certain brain or mental health conditions (like epilepsy, brain injury, bipolar disorder, schizophrenia, or current drug or alcohol problems)
- Are not taking certain medicines that can raise the risk of seizures (like stimulant medicines or high doses of bupropion)
- Do not have skin problems or injuries on your head that would make it hard to use our equipment
- Are not currently getting a certain treatment for Alzheimer’s disease (amyloid infusion)
- Have never fainted
- Can understand this form and agree to join, or have someone legally allowed to agree for you
- Do not have resting motor threshold over 61% of maximum stimulator output

3. Information about this research study

- If you decide to join, you will come to several sessions. You will play video games that use your brain signals. We will record your brain activity using sensors on your head (EEG). Sometimes, we will use TMS, which is a safe way to stimulate your brain, while you play the games. We will see how your brain signals and decisions change during these activities.
- You cannot join if you have any metal or electronic devices in or on your body.
- The risks in this study are about the same as in everyday life. You might feel some discomfort from the equipment or hear loud noises from the TMS. You might also feel tired after the sessions.

- During some sessions, you may see pictures that include nudity, violence, or blood.
- You will not get any direct benefit from joining this study.
- Joining is your choice. You do not have to take part, and you can stop at any time.
- You will find more details later in this form. Please read everything carefully and ask us any questions you have before you decide whether to join.

What is the study about and why are we doing it?

Cognitive decline affects a significant proportion of our society as a consequence of natural longevity or pathological neurodegenerative processes and remains a challenge in clinical neuroscience. Specific areas of cognitive decline typically involve memory and cognitive control.

A promising new avenue to prevent cognitive decline is the use of transcranial magnetic stimulation (TMS), which is a noninvasive procedure that uses magnetic fields to stimulate nerve cells in the brain. Recent TMS studies have shown to enhance cognitive functions such as working memory, associative memory in healthy and memory impaired patients.

Based on previous literature and our own work, we would like to test the hypothesis that an investigational closed-loop TMS, where brain stimulation is triggered by personalized patterns of subject's brain activity detected by a brain-computer interface (BCI), will have superior efficacy and therapeutic benefits compared to open-loop TMS. The word "investigational" means the study TMS device is still being tested in research studies and is not approved by the U.S. Food and Drug Administration (FDA) for this use.

In this study, you will participate in 15 sessions spread over 9 days, where the first eight days will be within two weeks and the ninth day will be eight weeks after the eighth day. The 15 sessions consist of 3 sessions with cognitive assessments plus BCI calibrations and 12 BCI-TMS sessions. The battery of cognitive assessments and the BCI calibration will be administered on the same day (battery sessions) and BCI-TMS sessions will be administered twice per day. Prior to the BCI-TMS session you will be randomly assigned to receive either closed-loop or open-loop TMS. During the BCI-TMS sessions, you will play engaging video games requiring cognitive control composed of 8 blocks. The 3 battery sessions will take place on the first day, on the eighth day (immediately after the end of the BCI-TMS sessions), and eight weeks after the eighth day in order to evaluate the effectiveness of the BCI-TMS intervention with respect to time course. Further details about each of the procedures is explained in the 'What will happen if you take part in this study?' section. Data collected from will be used to evaluate the effectiveness of the BCI-TMS in terms of cognitive performance and age-related decline.

Progress achieved in this study will allow the development of more effective brain stimulation methods for people with memory disorders such as mild cognitive impairment and Alzheimer's disease.

What will happen if you take part in this study?

If you agree to take part in this study, you will be asked to participate in 15 sessions so that we can assess the effect of the brain stimulation protocol on your EEG and cognitive performance:

- Cognitive assessment. Total duration: One hour. Location: Dr. Millán's laboratory at the Dell Medical School - Health Discovery Building. In these sessions, you will be administered standard memory tests and the Affective Flexibility task. During the Affective Flexibility task, you will be presented with a series of affective pictures and asked to sort the pictures based on either an affective rule or a neutral rule. More detailed instructions about these tests will be given during the cognitive assessment sessions. These cognitive assessments will be conducted by trained personnel three times, once before the BCI-TMS sessions, once after the BCI-TMS sessions and once 8 weeks after the BCI-TMS sessions. These sessions will be administered on the same day as the BCI calibration.

- BCI calibration session. Total duration: 1 hour and 40 minutes on first session, 1hour on rest of the sessions. Location: Dr. Millán's laboratory at the Dell Medical School - Health Discovery Building.

    - Resting motor threshold (RMT) measurement: At the beginning of the first session, we will determine your RMT. The RMT is a standard measure used in brain stimulation studies to identify the minimum stimulation intensity needed to produce a small, involuntary movement in a hand or finger muscle. To find this threshold, short magnetic pulses will be delivered to your scalp one at a time. After each pulse, we will observe whether a small hand or finger movement occurs or whether the muscle sensor detects activity. If your RMT is higher than the maximum intensity that our stimulator can safely deliver, it may not be feasible to continue with the remainder of the study procedures. In that case, your participation will end at that point, and you will be compensated for your visit.

    - Behavioral run: We will first start with a behavioral run to make sure you understand how to perform the task before any device setup. The task is to play a video game that requires you to attend and respond to some events but to ignore other distractor events (this is called "cognitive control"). On the very first BCI calibration session, the researcher will instruct you about the task, but you are free to ask any question until you clearly understand the rules of the task. Duration: 5 minutes.

    - Setup: You will be set up with 32-channel EEG, electrooculogram (EOG), electromyogram (EMG), and an 8-shaped TMS coil. Once this is done, we will ask you to blink, move your eyes horizontally and vertically, and roll your eyes in clockwise/counterclockwise directions as shown on the screen to measure your muscular signals while you are moving your eyes. Afterwards we will stimulate your brain with the TMS to measure your resting motor threshold with the EMG. Duration: 35 minutes.

    - BCI calibration: These calibrations will consist of four runs, five minutes each, where you will be instructed to perform the cognitive control task you played in

the Behavioral run but this time with the EEG and EOG recording. You are welcome to take a break between the runs if you get tired. Duration: 20 minutes.

- BCI-TMS session. Total duration: 30-60 minutes. Location: Dr. Millan's laboratory at the Dell Medical School - Health Discovery Building. The BCI-TMS sessions will consist of the following:
    - Behavioral run: Identical to the Behavioral run procedure in the BCI calibration section.
    - Setup: Identical to the Setup procedure in the BCI calibration section.
    - BCI-TMS runs: There will be 4 or 8 runs, five minutes for each run, where you will perform the cognitive control task you played in the BCI calibration but this time you will be delivered TMS prior to or while performing the task with the stimulation modality depending on your assigned group. You are welcome to take a break between the runs if you get tired. Duration: 25-60 minutes.
    - Removal: You will be doffed EEG, EMG, EOG, TMS and can wash off the gel. This step will be done only after the second BCI-TMS session. Duration: 2 minutes.

The following is the sequence in which the sessions mentioned above will be carried out:

I. Day 1: Baseline
    A. Cognitive assessment
    B. BCI calibration session

II. Days 2-7: Intervention
    A. BCI-TMS session
    B. Break (minimum 50 minutes)
    C. BCI-TMS session

III. Day 8: Post-stimulation
    A. Cognitive assessment
    B. BCI calibration session

IV. Day 9: Eight weeks follow-up
    A. Cognitive assessment
    B. BCI calibration session

How long will you be in this study and how many people will be in the study?

This study will consist of 15 sessions – 14 sessions that happen within two weeks and one additional follow-up session which will be conducted eight weeks after the 14th session. We plan to enroll 60 cognitively unimpaired young (18-35 years old) and 60 older (60-90 years old) adult subjects.

What risks and discomforts might you experience from being in this study?

You may experience some risks and/or discomforts from being in this study. They are:

- After EEG recording, you will need to wash your hair to remove the gel.
- EOG and EMG electrodes are sticky and may cause a rash when adhered.
- During TMS you may have unpleasant sensations such as tingling sensation and muscular tension of the stimulated area, and researchers will adjust the stimulation parameters to avoid or, at least, minimize them.
- There is <0.02% overall risk of seizure related to TMS delivery. Seizure is more likely to occur in individuals who have a personal or family history of epilepsy/seizure brain damage.
- If you have a history of fainting, you may be more likely to experience lightheadedness or fainting during TMS and will be excluded from participation.
- You may experience loud noise from the TMS and you will wear earbuds during the BCI-TMS sessions.
- A moderate fatigue will be possible after the experiment, comparable to a normal exercise or playing a computer game.
- During the cognitive assessment sessions, you will be shown explicit images that may contain nudity, violence, or gore. If you are uncomfortable and wish to stop viewing the images, you will be able to do so.
- Participation in research might involve some loss of privacy. There is risk that someone outside the research study could see and misuse information about you. More information about how we will protect your information to reduce this risk can be found below.
- Closed-loop TMS involves risks that are currently unknown or unforeseeable.

The researchers will let you know about any significant new findings (such as additional risks or discomforts) that might make you change your mind about participating in this study.

How could you benefit from this study?

There is no guarantee that you will receive any benefits from being in this study. It is possible that the tested protocols may lead to beneficial central nervous system plasticity and improved cognitive function. In addition to this, the progress achieved in this study will allow the development of more effective brain stimulation methods as a general societal benefit for people with memory disorders such as mild cognitive impairment and Alzheimer’s disease.

What will happen to the samples and/or data we collect from you?

We will collect your EEG, EMG, and EOG signals. All these data will be confidential, as it will not contain information that can identify you.

How will we protect your information?

We will protect your information by using anonymous participant codes. Your name and any other information that can directly identify you (like signed consent forms) will be stored separately from the data collected as part of the project. Master keys with the participant codes will be kept in a locked cabinet and separated from the signed consent forms that will be kept in a locked cabinet.

We will share your data with other researchers for future research studies that may be similar to this study or may be very different. The data shared with other researchers will not include information that can directly identify you.

We plan to publish the results of this study. To protect your privacy, we will not include any information that could directly identify you.

Under certain situations, we may break confidentiality. If during the study, we learn about child or elder abuse or neglect, we will report the information to the appropriate authorities, including the police and/or the Texas Department of Family and Protective Services.

Information about you may be given to the following organizations: Representatives of UT Austin and the UT Austin Institutional Review Board, Officials of the Department of Health and Human Services or the Federal Food and Drug Administration.

A description of this study 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.

What will happen to the information we collect about you after the study is over?

We will keep your research data to use for future research. Your name and other information that can directly identify you will be deleted from the research data collected as part of the project. The master key will be destroyed 6 months after the study analysis is completed. The signed consent forms will be destroyed 3 years after the study is completed.

What if we learn something about your health that you did not know?

As part of this study, we may learn medically relevant information about you. If we learn something that you and your doctor did not know, we will contact and inform you of the findings in person at the next scheduled session or in a phone call if you finished the study. Dr. Millán will also write a letter. With your permission, the findings will also be reported to your physician. Our research team, including the qualified medical doctors and The University of Texas at Austin, are not responsible for any medical exam or treatment.

How will we compensate you for being part of the study?

You will receive compensation in the form of Tango cards. Compensation will occur at the end of the last session you've participated in. You will be responsible for any taxes assessed on the compensation.

You will receive compensation in the amount of $20 per session for your participation in this study. If you withdraw from the research before the end of the study, you will be compensated within a week after the last day you have participated in.

We will also cover your parking passes at the Health Center Garage for every visit.

Who will pay if you are hurt during the study?

In the event of a research-related injury, it is important that you notify the Principal Investigator of the research-related injury immediately. You and/or your insurance company or health care plan may be responsible for any charges related to research-related injuries. Compensation for an injury resulting from your participation in this research is not available from The University of Texas at Austin.

You are not waiving any of your legal rights by participating in this study.

Your Participation in this Study is Voluntary

It is totally up to you to decide to be in this research study. Participating in this study is voluntary. Your decision to participate will not affect your relationship with The University of Texas at Austin, your doctor, and your healthcare provider. Even if you decide to be part of the study now, you may change your mind and stop at any time. You do not have to answer any questions you do not want to answer. Your decision not to take part or to withdraw will involve no penalty or loss of benefits to which you are otherwise entitled.

The Food and Drug Administration requires that we keep a record of your involvement with the study. Even if you leave the study, we must keep the data we have already collected.

Contact Information for the Study Team

If you have any questions about this research, you may contact:

Prof. José del R. Millán
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Or

Prof. Jared Benge
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Contact Information for Questions about Your Rights as a Research Participant

If you have questions about your rights as a research participant, or wish to obtain information, ask questions, or discuss any concerns about this study with someone other than the researcher(s), please contact the following:

The University of Texas at Austin Institutional Review Board

Phone: 512-232-1543
Email: irb@austin.utexas.edu

Please reference the protocol number found at the top of this document.

Your Consent

By signing this document, you are agreeing to be in this study. We will give you a copy of this document for your records. We will keep a copy with the study records. If you have any questions about the study after you sign this document, you can contact the study team using the information provided above.

I understand what the study is about and my questions so far have been answered. I agree to take part in this study.

_____

Printed Subject Name

_____

Signature Date

_____

Signature of Person Obtaining Consent Date