Official Study Title: Cognitive Enhancement in Depression (The COG-D Study)
NCT #: 05400512
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Version: 7.0
Date: June 10, 2024
PI: Sarah M. Szymkowicz, PhD

Name of participant: _____ Age: _____

The following is given to you to tell you about this research study. Please read this form with care and ask any questions you may have about this study. Your questions will be answered. Also, you will be given a copy of this consent form.

Key Information:
The first section of this document contains some key points that the research team thought you would find important. The study is described in more detail after this section. If you do not understand something, please ask someone.

Key information about this study:

What is the purpose of this study?

The purpose of this study is to better understand whether a combination of non-pharmacological approaches can improve memory and thinking, as well as depressive symptoms, in older individuals with recurrent depression. The non-pharmacological approaches we are investigating include transcranial direct current stimulation (tDCS) and computerized cognitive training. tDCS uses small currents of electricity on your forehead to potentially stimulate your brain's ability to process and learn. Computerized cognitive training uses computer or tablet games to improve memory and thinking. We also want to determine how tDCS and computerized cognitive training affects brain function in order to cause these changes. To date, there is no medicine or intervention that is approved by the U.S. Food and Drug Administration (FDA) to treat memory and thinking difficulties in depressed adults.

We are examining tDCS and computerized cognitive training in this study because past research suggests that these interventions individually may improve thinking skills and depression. Previous pilot work combining these interventions in older adults without depression found encouraging results, such that the application of active tDCS during cognitive training improved outcomes to a greater extent than sham tDCS paired with cognitive training. In this study, we will apply tDCS to both sides of your forehead, which is not approved for the treatment of depression by the U.S. FDA and is thus considered an experimental procedure.

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What will happen and how long will you be in the study?

If you agree to be in this study, you will first be asked to sign and date this consent form. The study takes place over the course of at least 18 weeks. After we determine you are eligible to participate in the study, you will complete a baseline visit, 4 weeks of daily intervention visits, a post-intervention visit, and then a 3-month follow-up visit. **Note that participants will be randomized to receive either active or sham (i.e., placebo) tDCS and all participants will receive the cognitive training intervention.**

To be eligible for this study, you will need to have a history of recurrent depression (defined as 2 or more depressive episodes – either currently or within the past 3 years). This will be determined via a structured clinical interview. Regarding treatment, you may participate if you are taking a therapeutic dose of an allowable antidepressant medication. You will be asked to continue that medication throughout the study. If you are not taking an antidepressant medication(s), you may still be eligible to participate. If you are taking a medication that is not allowed, you may be eligible for a separate study that includes treatment with antidepressant medications.

This study involves multiple in-person visits:

- Screening visit to determine study eligibility
- Baseline visit (to complete initial assessments)
- Intervention visits (to occur 5 days / week for 4 weeks, or 20 visits)
- Post-intervention visit (at week 5 to repeat assessments)
- 3-month follow-up (at week 17 to repeat assessments)

Additionally, you will complete 2 brain scans (at baseline and week 5). The brain scans are done using Magnetic Resonance Imaging (MRI) and do not involve radiation exposure. We will screen you to determine whether you are safe to undergo an MRI.

To determine study eligibility, a clinical assessment and other screening measures will be completed, as well as the first half of memory and thinking testing. This visit will take 3.0 – 3.5 hours. Before starting the intervention, you will complete the second half of memory and thinking testing, complete some questionnaires, as well as undergo a brain MRI scan. This visit can take up to 3.5 hours total and may be split up over several days. The intervention will occur daily (5 days / week) for 1.5 hours over the course of 4 weeks. You will then repeat the memory and thinking testing, questionnaires, and the brain scan at week 5 and only the memory and thinking testing and questionnaires at week 17. The week 5 visit will take up to 4.0 hours and the week 17 visit will take up to 3.0 hours.

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The total amount of time you may spend at in-person study visits is about 44 hours. Study visits will be discussed in more detail in the next section of this document.

Detailed Information:
The rest of this document includes detailed information about this study (in addition to the information listed above).

You are being asked to take part in this research study because you have recurrent depression and are age 60 years or older.

You do not have to be in this research study. You may choose not to be in this study and get other treatments without changing your healthcare, services, or other rights. You can stop being in this study at any time. If we learn something new that may affect the risks or benefits of this study, you will be told so that you can decide whether or not you still want to be in this study. Your medical record will contain a note saying you are in a research study and may contain some research information about you. Anyone you authorize to receive your medical record will also get this information.

Side effects and risks that you can expect if you take part in this study:

Diagnostic, Cognitive Testing, and Clinical Interviews: You may experience boredom or discomfort during the clinical interview and evaluations when discussing symptoms and recent life events. You may also experience frustration with some cognitive (i.e., memory and thinking) tasks. Should you wish to stop or take a break, the study staff will allow it.

Should you express suicidal ideation at any time during the interview or intervention, Dr. Szymkowicz or another study doctor will be contacted to assess you and to determine appropriate course of treatment. Thoughts of suicide will be taken very seriously.

Worsening Depressive Symptoms: It is possible your depressive symptoms may worsen and suicidal ideation develop during the course of your participation in this study. We are reducing this risk by allowing all participants to engage in the cognitive training, which has been shown to improve mood / depressive symptoms. We will frequently monitor depressive symptoms and be available for phone calls or urgent in-person visits for worsening depression. If you exhibit worsening depressive symptoms, you may be withdrawn from the study and referred for appropriate clinical care.

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Risks of Magnetic Resonance Imaging (MRI): There are no known major risks with an MRI scan. But it is possible that harmful effects could be found out in the future. Even though the tunnel is open, it may bother you to be placed in a tight space (claustrophobia), and to hear the noise made by the magnet during the scan. You will be given earplugs to reduce the noise. You may also feel the table vibrate and / or move slightly during the scan. It may be hard to lie on the table during the scan. If you have any metal pieces in your body, they could move during the scan and damage nearby tissues or organs.

Transcranial Direct Current Stimulation (tDCS) Side Effects: You may experience itching and tingling or mild discomfort at the area of stimulation and headache. Other possible side effects include dizziness and nausea. Whenever an electrical stimulation is applied to the body, it could possibly cause a seizure or abnormal heartbeat, but this has never occurred with the tDCS parameters used in this study. The application of electrical current to the brain does induce functional changes (i.e., neural plasticity) that can present as a potential risk.

Computerized Cognitive Training Side Effects: You may find cognitive training on the computer challenging, fatiguing, and / or boring. You may also feel fatigued during the cognitive training sessions and breaks will be allowed as needed. Research staff will explain what to do and how to perform the training tasks tests during the initial study visit. Study staff will also be available at each training session to assist with troubleshooting.

Loss of Confidentiality: There is also the potential risk of loss of confidentiality. Every effort will be made to keep your information confidential; however, this cannot be guaranteed.

Risks that are not known:

As with any research, there may be risks of participation or from the study interventions that we cannot predict. Because the tDCS intervention is investigational, meaning non-FDA approved, there may be risks that we do not know about at this time. If you experience any unpleasant effects during this study not mentioned in this consent form, please contact study staff or the study doctor as soon as possible.

Good effects that might result from this study:

The benefits to science and humankind that might result from this study: You will be adding to the understanding of whether the combination of tDCS and computerized cognitive training may help treat cognitive difficulties and depressive symptoms in older adults. This information will help us

determine if the combination of interventions may be a useful approach to treating memory and thinking problems in older individuals with recurrent depression.

The benefits you might get from being in this study: By undergoing the tDCS and computerized cognitive training intervention, you may experience improvement in your memory and thinking functioning. You may also experience an improvement in depressive symptoms, if present. However, as people respond differently to treatments, personal benefit cannot be guaranteed.

Procedures to be followed:

Screening Visit (Total Time: 3.0 to 3.5 hours):
During the initial visit, you will meet with a study doctor and / or study staff. Your medical and psychiatric history will be carefully reviewed to make sure that you are eligible for the study. Additionally, we will assess your current depressive symptoms and your current and past medication use. You do not have to answer any questions you do not feel comfortable answering. You will also complete the first half of the memory and thinking testing (further described below). The interview and cognitive testing will take 3.0 to 3.5 hours total (either all with the study doctor or 2.0 to 2.5 hours with study staff and 1.0 hour with the study doctor).

For your safety, you must tell a study doctor about all the medications you are taking, including over-the-counter drugs and herbals, before you start the study. If there is a problem where you cannot be in the study because of one of the medications you are taking, a study doctor will discuss that with you.

As part of this visit, we will carefully evaluate you to determine if you have any metal in your body that could stop you from having the MRI. If you have had any surgeries that used implanted metal objects, we will need to see the card or pamphlet you were given explaining the MRI risks of that object. If you do not have the card / pamphlet, we will need to request medical records to assure your safety before you could proceed to MRI. If we are unable to determine the safety of an implanted metal object, you will not be eligible to participate in this study.

During this visit, you will also have an option to complete a "mock" MRI scan. Although no actual scan is taken, you will be able to experience the process (getting on and off the table, being inside the tube, and hearing the sounds the machine produces during a scan) to make sure you are comfortable having an MRI scan.

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We will administer a questionnaire determining history of COVID-19 exposure and associated treatments prior to entry into the study, following completion of the 4-week intervention, and at the 3-month follow-up visit. Exposure to, and treatment for, COVID-19 is not exclusionary; rather, we are collecting this information for documentation purposes, as having COVID-19 may affect memory and thinking in some individuals and we want to be able to account for this when trying to understand results of the intervention.

Baseline Visit (Total Time: 3.0 to 3.5 hours)
After we are sure that you are safe to complete the MRI (to be determined during the screening visit), you will be scheduled for an in-person baseline visit. You will meet with a study doctor and / or study staff who will again assess your depressive symptoms. During that visit, you will complete the second half of the cognitive (memory and thinking) testing (described below), fill out questionnaires about your mood and other related symptoms, and undergo the MRI scan. This visit can last about 3.0 – 3.5 hours. If needed, we can spread the procedures out over two (2) days, as long as both visits occur within fourteen (14) days of each other.

Cognitive (Memory and Thinking) Testing: We will ask you to complete some tasks that measure your attention, memory, and other cognitive / thinking abilities. These tasks will be completed both on a computer and via paper and pencil measures. These tasks will occur in several phases:

- You will complete the first half of cognitive testing at the screening visit (~1.0 hour) and the second half at the baseline visit (~1.0 hour)
- At your subsequent visits, cognitive testing will occur at the end of the 4-week intervention phase (at week 5 for about 2.0 hours) and again at the 3-month follow-up visit (at week 17 for about 2.0 hours).

The cognitive testing is completed for **research purposes only** and you **will not** receive clinical interpretation of your performance.

MRI: You will complete two (2) brain scans using Magnetic Resonance Imaging (MRI) – one before starting the intervention and one following completion of the intervention.

Each MRI scan will take about 60 minutes. MRI scans occur in a large machine that is shaped like a tunnel. This scan does not use x-rays. Instead, a strong magnet and radio waves, like those used in an AM / FM radio, are used to make pictures of your body.

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During the MRI scan, you will complete a task that measures attention and short-term memory. This task shows you different letters and you will have to identify whether the current letter is the same or different from a previously shown letter (depending on the condition).

You will be able to practice the task and ask questions about them prior to entering the MRI.

You may not be able to have this scan if you have a device in your body, such as aneurysm clips in your brain, heart pacemakers or defibrillators, or cochlear (inner ear) implants. Also, you may not be able to have this scan if you have iron-based tattoos or pieces of metal (e.g., bullet, BB, shrapnel) close to or in an important organ (such as the eye). If we determine that you cannot safely complete the MRI, we will withdraw you from the study.

Certain metal objects, like watches, credit cards, hairpins, writing pens, etc., may be damaged by the MRI machine or may be pulled away from the body when you are getting the scan. Also, metal can sometimes cause poor pictures if it is close to the body part being scanned. For these reasons, you will be asked to remove these objects before going into the room for the scan.

You will hear hammering, clicking, or squealing noises during the scan. You will be given earplugs to reduce the noise. You will also be told how to alert the staff if you need them.

During the scan, the MRI staff is able to hear and talk to you in between scans. You will also be able to hear the staff in between scans. They will be talking to you throughout the scanning process and may ask you to not move or do other simple tasks. You may be asked to lie very still throughout the scan.

In this study, **the MRI scan is for research only**. However, if we see something that is not normal, you will be told and asked to consult your doctor. The scans will not be routinely examined by health professionals for potential abnormalities. However, in the event an abnormality is detected by the investigators or the MRI technologist, the scans will be further examined by a radiologist and the investigator may encourage you to consult your physician or provider referrals for further evaluations.

The MRI scanner has been used with research animals. For your safety, we clean the scanner with bleach before and after your scan as we do with scanners used only for humans.

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Intervention (Total Time: 1.5 hours / day for 4 weeks aka 20 visits)
Participants will be randomized to receive either active or sham (i.e., placebo) tDCS to occur during the first 20-minutes of cognitive training and everyone will complete the 50-minute computerized cognitive training intervention. At each intervention visit, we will administer a brief symptom screening questionnaire at the beginning (symptoms in the past 24 hours) and at the end (symptoms during stimulation). Weekly, we will assess your depressive symptoms. At the end of the intervention, we will administer questionnaire asking whether you believe you were in the active or sham tDCS condition.

Example of tDCS electrode set-up and device

Post-Intervention, Week 5 (Total Time: 3.5 to 4.0 hours)
During week 5, an in-person study visit will be scheduled. At this visit, all of the cognitive testing will be repeated and you will be asked to complete a series of questionnaires assessing depression, mood, and overall functioning, similar to what was completed at the screening and baseline visits. You will also have the second 60-minute MRI.

3-Month Follow-Up, Week 17 (Total Time: 2.5 to 3.0 hours)
Week 17 will be your final visit for this study. This visit will include completion of the cognitive testing and the series of questionnaires. You will discuss any intervention side effects with a study doctor. This visit will be completed in-person.

Visit Type	Approximate Time	Study Doctor Visit	Cognitive Testing	Questionnaires	MRI	tDCS + CCT
Screening	3.0 to 3.5 hrs	X	X	X		
Baseline (week 0)	3.0 to 3.5 hrs	X	X	X	X	
Intervention (weeks 1 to 4)	1.5 hrs / day for 4 wks			X		X
Post-Intervention (week 5)	3.5 to 4.0 hrs	X	X	X	X	
3-Month Follow-Up (week 17)	2.5 to 3.0 hrs	X	X	X		

hrs = hours, wks = weeks, MRI = magnetic resonance imaging, tDCS = transcranial direct current stimulation, CCT = computerized cognitive training

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Other treatments you could get if you decide not to be in this study:

You do not have to participate in this study to receive treatment for depression. There are many antidepressants that are commercially available and may be prescribed by your physician. Talk therapy is also available, which is a treatment for depression that does not require medications. You may also be eligible for other research studies. If you have any questions about these options, a study doctor will discuss them with you.

Payments for your time spent taking part in this study or expenses:

You will be compensated for your participation based on how many visits / assessments you attend. You can receive up to $575. The table below shows how much you will receive for completing each visit:

Visit	Amount
Screening	$25
Baseline (Week 0)	
Cognitive Testing	$50
MRI	$100
Intervention (Weeks 1 to 4, full participation / completion)	$200 ($10 / day for 4 weeks)
Post-Intervention (Week 5)	
Cognitive Testing	$50
MRI	$100
3-Month Follow-Up (Week 17)	
Cognitive Testing	$50
Total	**Up to $575**

We will ask for your Social Security Number (SSN) and address before you are compensated for taking part in this study.

Costs to you if you take part in this study:

There is no cost to you for taking part in this study.

Payment in case you are injured because of this research study:

If it is determined by Vanderbilt and the Investigator that an injury occurred as a direct result of the tests or treatments that are done for research, then you and/or your insurance will not have to pay for the cost of immediate medical care provided **at Vanderbilt** to treat the injury.

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There are no plans for Vanderbilt to pay for any injury caused by the usual care you would normally receive for treating your illness or the costs of any additional care. There are no plans for Vanderbilt to give you money for the injury.

Who to call for any questions or in case you are injured:

If you should have any questions about this research study or if you feel you have been hurt by being a part of this study, please feel free to contact the principal investigator, Dr. Sarah Szymkowicz, at (615) 875-0032.

For additional information about giving consent or your rights as a person in this study, to discuss problems, concerns, and questions, or to offer input, please feel free to call the VUMC Institutional Review Board Office at (615) 322-2918 or toll free at (866) 224-8273.

Reasons why you may be taken out of this study:

Your study clinician may withdraw you from study participation if she or he determines that, based on the initial study interview, you are not eligible to continue the study. She or he may also withdraw you if you are having difficulty completing study procedures, if you need an immediate referral for clinical care, or if she / he decides that it is not in your best interest to continue in the study. If you are taken out of the study, you will be told the reason.

What will happen if you decide to stop being in this study?

If you decide to stop being part of the study, you should tell your study doctor. We may ask you to come in for a final study visit. If you withdraw or are withdrawn from the study early, you will be compensated for the parts of the study you have completed.

All participation in the study is voluntary and there is no penalty for refusing to participate or for early withdrawal. Deciding to not be part of the study will not change your regular medical care in any way.

Clinical Trials Registry:

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 Web site at any time.

Confidentiality:

All reasonable efforts will be made to keep the personal information in your research record private and confidential, but absolute confidentiality cannot be guaranteed. Your records will be kept in

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locked filing cabinets within locked rooms and only the research team will have access. Your information may be shared with institutional and / or governmental authorities, such as the Vanderbilt University Institutional Review Board, if you or someone else is in danger or if we are required to do so by law.

All data are labeled and coded for protection and confidentiality. Data are kept on secure, password protected networked computers and in locked offices. Identification numbers are used instead of names for additional protection. Only research staff will have access to participant data. Source materials will be labeled and coded with an identification number that is not linked in any way to participant personal identifying information for purposes of additional protections and confidentiality. This number will be used to identify participants' self-reported questionnaires, cognitive results, and MRI / fMRI computerized data.

A list linking names to identification numbers will be available only to authorized personnel and will be kept separately from research charts. Only research personnel authorized by the Principal Investigator will have access to these records. The link between your identity and your identification number will not be shared with researchers in other institutions and will not leave VUMC.

During the study, if we learn you are having thoughts about suicide or hurting yourself or others, the research staff will ask you more questions about your thoughts. Based on your responses, the staff may provide you with help to get treatment. This may include:

- Working with you to contact your doctor,
- Contact a trusted family member or therapist to discuss your thoughts,
- Or work with you on a plan that may include getting you to a hospital for safety.

In these cases, the research team may share information about your condition with other health care providers.

Vanderbilt may share your information, without identifiers, to others or use it for other research projects not listed in this form. Vanderbilt, Dr. Szymkowicz, and her staff will comply with any and all laws regarding the privacy of such information. There are no plans to pay you for the use or transfer of this de-identified information.

Data from the computerized cognitive training program will be leaving Vanderbilt University Medical Center for storage and analysis. Other data may be shared with the University of Utah as needed (e.g., relevant demographic information, treatment group, etc.). These data will be deidentified, meaning

that they will only include your study-created identification number. No direct participant identifiers will leave Vanderbilt University Medical Center.

Privacy:

Any samples and information about you may be made available to others to use for research. As the creator of the propriety software used for the cognitive training intervention is located at the University of Utah, study information about you will be shared with this study investigator at the University of Utah. To protect your privacy, we will not release your name or other direct identifiers.

You will not receive any benefit as a result of the tests done on your samples. These tests may help us or other researchers learn more about the causes, risks, treatments, or how to prevent this and other health problems.

Your samples may be used to make new products or tests. These may have value and may be developed and owned by the study staff, Vanderbilt University, Vanderbilt University Medical Center, and/or others. If this happens, there are no plans to provide money to you.

Study Results:

You will not receive results from the study. However, you will know how the intervention affects you. If it would help your medical care, we can provide copies of your MRI scan to your physician. This would be a copy of the images, not a radiologist report.

Authorization to Use/Disclose Protected Health Information

What information is being collected, used, or shared?

To do this research, we will need to collect, use, and share your private health information. By signing this document, you agree that your health care providers (including both Vanderbilt University Medical Center and others) may release your private health information to us, and that we may use any and all of your information that the study team believes it needs to conduct the study. Your private information may include things learned from the procedures described in this consent form, as well as information from your medical record (which may include information such as HIV status, drug, alcohol or STD treatment, genetic test results, or mental health treatment).

Who will see, use or share the information?

The people who may request, receive or use your private health information include the researchers and their staff. Additionally, we may share your information with other people at Vanderbilt, for

example if needed for your clinical care or study oversight. By signing this form, you give permission to the research team to share your information with others outside of Vanderbilt University Medical Center. This may include the sponsor of the study and its agents or contractors, outside providers, study safety monitors, government agencies, other sites in the study, data managers and other agents and contractors used by the study team. We try to make sure that everyone who sees your information keeps it confidential, but we cannot guarantee that your information will not be shared with others. If your information is disclosed by your health care providers or the research team to others, federal and state confidentiality laws may no longer protect it.

Do you have to sign this Authorization?
You do not have to sign this Authorization, but if you do not, you may not join the study.

How long will your information be used or shared?
Your Authorization for the collection, use, and sharing of your information does not expire. Additionally, you agree that your information may be used for similar or related future research studies.

The study results will be kept in your research record for at least six (6) years after the study is finished. At that time, the research data that has not been put in your medical record will be kept for an unknown length of time. Any research data that has been put into your medical record will be kept for an unknown length of time.

What if you change your mind?
Unless told otherwise, your consent to use or share your PHI does not expire. You may change your mind and cancel this Authorization at any time. If you cancel, you must contact the Principal Investigator in writing to let them know. The mailing address is 1601 23rd Avenue South, Nashville, TN 37212. At that time, we will stop getting any more data about you. Your cancellation will not affect information already collected in the study, or information that has already been shared with others before you cancelled your authorization. The health data we stored before you withdrew your consent may still be used for reporting and research quality.

If you decide not to take part in this research study, it will not affect your treatment, payment or enrollment in any health plans or affect your ability to get benefits. You will get a copy of this form after it is signed.

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STATEMENT BY PERSON AGREEING TO BE IN THIS STUDY

I have read this consent form and the research study has been explained to me verbally. All my questions have been answered, and I freely and voluntarily choose to take part in this study.

_____ _____
Date Signature of patient/volunteer

Consent obtained by:

_____ _____
Date Signature

_____
Printed Name and Title

Time: _____

With respect to being contacted about other studies happening in the Vanderbilt Center for Cognitive Medicine that I may be eligible for, please sign your initials next to your preferred choice:

_____ I DO consent to be contacted about other studies (at which time I can choose whether not I would like to participate).

or

_____ I DO NOT consent to be contacted about other studies.