Participant Information Sheet

Study title: Effect of brain stimulation on cognitive functioning and pain.

Locality: Dunedin School of Medicine, University of Otago, New Zealand.

Ethics committee ref.: 19/STH/197

Lead investigator(s): Dr. Divya Adhia & Professor Dirk De Ridder

Contact phone number: 03 470 9337

You are invited to take part in a study on the effect of brain stimulation on cognitive functioning (e.g., memory) and pain. Whether or not you take part is your choice. If you don't want to take part, you don't have to give a reason, and it won't affect the care you receive. If you do want to take part now, but change your mind later, you can pull out of the study at any time.

This Participant Information Sheet will help you decide if you'd like to take part. It sets out why we are doing the study, what your participation would involve, what the benefits and risks to you might be, and what would happen after the study ends. We will go through this information with you and answer any questions you may have. You do not have to decide today whether or not you will participate in this study. Before you decide, you may want to talk about the study with other people, such as family, whānau, friends, or healthcare providers. Feel free to do this.

If you agree to take part in this study, you will be asked to sign the Consent Form on the last page of this document. You will be given a copy of both the Participant Information Sheet and the Consent Form to keep.

This document is eight pages long, including the Consent Form. Please make sure you have read and understood all the pages.

WHAT IS THE PURPOSE OF THE STUDY?

The purpose of this study is to explore the effect of a non-invasive external brain stimulation technique [Transcranial current stimulation (TCS)] on cognitive functioning (e.g., memory, reaction time) and experimental pain measures (e.g., sensitivity to pressure/pain sensation) in healthy middle-aged and older adults. Different regions of our brain work together synchronously, such that some areas of the brain are activated, and others are deactivated (i.e., anti-correlated patterns) based on a particular task. This study will compare the effects of stimulating a single brain region versus simultaneously stimulating two brain regions in their anti-correlated pattern, on cognitive functioning and experimental pain measures. The findings from this study will help us determine if simultaneously targeting the anti-correlated activity of the different brain regions can improve cognitive functioning and pain measures.

The brain regions targeted in the current study have demonstrated to be altered in several neurological and neuropsychiatric conditions (e.g., Alzheimer's disease, traumatic brain

injury, schizophrenia, chronic pain, attention-deficit hyperactivity disorder, multiple sclerosis, and Parkinson's disease). The TCS has considerable potential as a treatment for these disorders due to its relatively low cost, safety, portability, and ease of use compared with other methods. The evidence obtained from this study will thus help us to develop novel interventions to improve health outcomes in various (above mentioned) clinical conditions.

WHO ARE WE SEEKING TO PARTICIPATE IN THE PROJECT?

We are seeking approximately 80 healthy individuals, aged between 35-75 years old, with no history of any pain or memory/cognitive problems.

You are not eligible to participate if you have the following condition(s): brain injury or disease (e.g. Stroke and Multiple Sclerosis), spinal cord injury or disease, nerve injuries or neuropathies in the limbs (having sensory loss/numbness and muscle weakness), soft-tissue injuries (in the last 3 months), epileptic seizures, unstable medical or psychiatric conditions, uncontrolled hypertension and heart failure, or history of acute myocardial infarction, presence of any pacemaker or defibrillator, presence of any implant in head/neck, presence of any pain/related condition (e.g. arthritis), alcohol or substance abuse, cold-sensitive conditions (e.g. Raynauld's disease, reflex sympathetic dystrophy), pregnancy or 6 months post-labor, skin conditions, and difficulty or inability to read English.

You will be screened for the conditions mentioned above by a research assistant, either by phone or by email, to determine your eligibility to participate in this study. You will also be asked to provide contact details of your GP or other current provider. The research assistant will contact your GP or other current provider if needed, to determine your eligibility for participation in the study, and to notify them if any diagnosable condition is recorded.

WHAT WILL MY PARTICIPATION IN THE STUDY INVOLVE?

You will be required to attend a single session of approximately 3.5 hours duration at the Dunedin School of Medicine. A female research fellow, with a health professional background, will administer the testing procedures. At the session, the protocol, as shown in Figure 1 below, will be administered, and will consist of the following phases:

- Baseline measurements
- Randomisation into treatment groups
- Stimulation treatment
- Post-treatment measurements

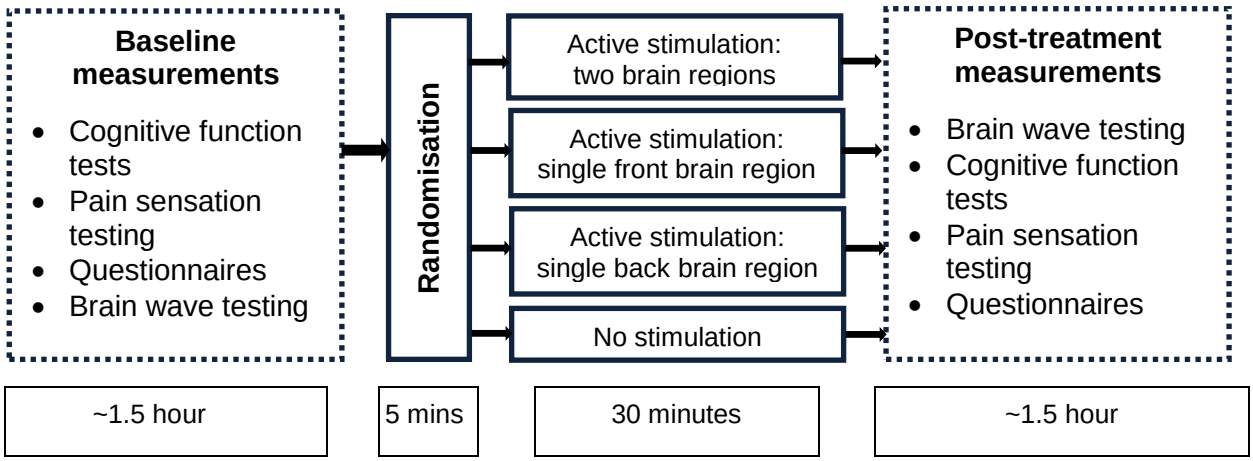

Figure 1. The study protocol and time-duration for each phase

Baseline measurements: The following tests will be conducted after obtaining written informed consent from the participants.

- **Cognitive testing:** You will be presented with words printed in different colors on a computer screen, and you will be asked to recognize the color and respond using one of the keys on the keyboard. Another testing will involve joining a trail of numbers/alphabets on a paper. Your memory will also be tested; you will be presented with a series of numbers, and you will be asked to repeat it back.
- **Pain sensation testing:** Following cognitive testing, simple test procedures recording your perception of pain sensation will be tested on your non-dominant wrist or leg region (just below the knee joint). You will be asked to bring shorts or pants that can be easily rolled up to knee level to expose your leg region for testing purposes. The following test procedures will be administered.
  - Repeated light touches with a thin and blunted nylon filament - You will be asked to tell us whether you are feeling a sensation of touch or pain. If you feel pain on repeated contacts, you will be asked to rate your intensity of pain on a 0-100 point scale.
  - The pressure to pain sensation testing - Pressure will be gradually applied by using a rubber-tipped pressure device. You will be asked to indicate immediately when the pressure sensation changes to discomfort or when you first feel pain. This procedure will be carried out when you are resting, as well as immediately following 2 minutes of hand immersion in a cold-water bath maintained at ~6^{o}C.
- **Questionnaires:** You will be asked to complete questionnaires about yourself (age, gender, education, ethnicity, and well-being), mood, cognition, and the presence of other health issues, if any (e.g., diabetes).
- **Brain wave testing:** After the above testing procedures, you will have to wear a cap on your head with 32 electrodes embedded into it. According to the Māori culture, the head is considered sacred *"he tapu te upoko"* and brain is regarded as the *wairua* (soul). The researcher conducting the testing will obtain permission from the participant at every stage before touching the participant's head. Electrode gel will be applied for recording better signal quality. The electrodes in the cap, which is connected to a computer, will record your brain activity when you are resting (for 10 minutes) with your eyes closed. The brain wave testing can be influenced by food and water intake. Hence, while participating in this study, we ask you not to eat any food or consume large amounts of water (e.g., 500 ml) for 2 hours before the testing. Additionally, we ask you to avoid smoking for 4 hours before testing. We also ask you not to perform any strenuous exercise or consume alcohol for at least 24 hours before testing.

Randomisation and treatment: Following the baseline assessment, you will be given a sealed envelope that will have your group information. You have equal chances of being randomised to one of the four treatment groups (i.e., No brain stimulation, Active stimulation to single brain region-front side, Active stimulation to single brain region-back side, or Active stimulation to two brain regions- front and back side). Please be prepared to be in either group when you sign up for the study. Based on your randomised group, the researcher will choose the stimulation program on the computer. The electrical stimulation protocol will be delivered for 30 minutes while you rest in a comfortable chair. You and the researcher conducting the assessments will not know which group you have been assigned to i.e., you will be blinded to your group allocation. This blinding is to eliminate a placebo effect of the stimulation. A placebo effect is the response of the participant that causes the observed

effect than the stimulation itself (i.e., a participant would respond differently when they know they are going to receive a stimulation, compared to when they are going to receive no-stimulation). The blinding will also enable us to determine whether any changes in the cognitive or pain testing measures and the brain waves are due to the brain stimulation.

Post-treatment measurements: Following the treatment protocol, the cognitive tests, pain sensation tests, mood questionnaire, and the brain wave testing will be repeated.

WHAT ARE THE POSSIBLE BENEFITS AND RISKS OF THIS STUDY?

Previous brain stimulation studies using TCS techniques have demonstrated that this technique is a safe and effective method for treating a number of clinical conditions (e.g., chronic pain, stroke). The most common side-effects reported by previous stimulation studies include headache, fatigue, nausea, insomnia, mild tingling sensation, and transient redness/itching under the stimulation electrodes. Most adverse effects are mild and disappear soon after stimulation. Other risks of participation include unexpected consequences of the neurostimulation itself, such as the onset of seizures. Stopping the stimulation should stop these side effects.

Your brain activity is recorded using the electrode cap, which is a safe and harmless procedure. Application of electrode gel may cause inconvenience, and you are offered to use the shower facilities at the hospital.

For pain testing, we do not anticipate any form of discomfort that would last following the test procedures. You may feel mild pain, tingling, or pins and needles sensation in your hand during or immediately following immersion in a cold-water bath. These ranges of sensations should usually disappear quickly following the testing. A slight reddening of the skin may stay following the pressure to pain sensation testing, and it should go within hours of testing.

You will be closely monitored for your responses during all the testing procedures, and sufficient rest periods will be provided between each testing procedure. Any side effects of training will be formally recorded and will be addressed if any medical attention is required.

Although, there will be no direct benefits to the participants themselves from participating in this study, the findings from this study will help us develop novel treatment techniques to improve health outcomes in individuals with cognitive problems (e.g., Alzheimer's Disease), and chronic pain.

WHO PAYS FOR THE STUDY?

The existing funds from the Neurological Foundation of New Zealand will cover the expenses associated with this study.

There will be no costs to you for participating in the study. You will receive a petrol voucher at the end of the session (value of $50) as a reimbursement for the travel/parking expenses associated with taking part in the study.

WHAT IF SOMETHING GOES WRONG?

If you were injured in this study, you would be eligible **to apply** for compensation from ACC just as you would be if you were injured in an accident at work or at home. This does not mean that your claim will automatically be accepted. You will have to lodge a claim with ACC, which may take some time to assess. If your claim is accepted, you will receive funding to assist in your recovery.

If you have private health or life insurance, you may wish to check with your insurer that taking part in this study won't affect your cover.

WHAT ARE MY RIGHTS?

- Your participation in this study is voluntary.
- You may withdraw from this project at any time and without any disadvantage to you of any kind. Besides, the study staff may decide to withdraw you from the study if you have any unexpected side effects from the treatment or if they have any other concerns.
- You have the right to access the information collected about you as part of the study.
- You will have full rights to correct or withdraw the information until the research is completed or until the time when we begin to analyse the data.
- We will inform you if any new information becomes available during the study that may impact on your health.

WHAT HAPPENS AFTER THE STUDY OR IF I CHANGE MY MIND?

As outlined above, we will collect various measures (e.g., memory, mood, response to pain testing, brain activity) by way of questionnaires and assessments. The data collected will be securely stored either in a locked filing cabinet or electronically with password protection, such that only those involved in the research program will be able to gain access to it. At the end of the project, any personal information will be destroyed immediately except that, as required by the University's research policy, any raw data on which the results of the project depend will be retained in secure storage for ten years, after which it will be destroyed.

The results of this study will be published in an international scientific journal. Only a summary of the gathered data will be mentioned in the research publication. The data included in the publication will in no way be linked to any specific person, and your identity will not be recorded with the data. At the testing session, you will be given a unique identification code, and your data will be linked to that code only. Only study personnel will have access to any personal information. Any personal information [such as names, contact details, email address] held on the participants for practical purposes during the study period will be destroyed once the study is completed. You are most welcome to request a copy of the results of the project should you wish. These will be available once all the data is analysed, approximately 1.5 years following the commencement of the study, nominally in the second quarter of 2021.

The data collected during this study might be made available to other researchers who are not connected with the current study for future use (e.g., to conduct additional analyses). All the data will be de-identified and linked to a unique identification study number, and no personal information will be shared.

WHO DO I CONTACT FOR MORE INFORMATION OR IF I HAVE CONCERNS?

If you have any questions, concerns, or complaints about the study at any stage, you can contact:

Name: Dr. Divya Adhia **Position**: Research Fellow **Department:** Department of Surgical Sciences, University of Otago, Dunedin.	**Phone number:** 03 470 9337 **Email**: divya.adhia@otago.ac.nz
Name: Professor Dirk De Ridder **Position**: Chair, Neurosurgery **Department:** Department of Surgical Sciences, University of Otago Dunedin.	**Phone number:** 03 470 9337 **Email**: dirk.deridder@otago.ac.nz
Name: Dr. Ramakrishnan Mani **Position**: Senior Lecturer **Department:** School of Physiotherapy, University of Otago, Dunedin	**Phone number:** 03 479 3485 **Email**: ramakrishnan.mani@otago.ac.nz

If you want to talk to someone who isn't involved with the study, you can contact an independent health and disability advocate on:

Phone: 0800 555 050
Fax: 0800 2 SUPPORT (0800 2787 7678).
Email: advocacy@advocacy.org.nz
Website: https://www.advocacy.org.nz/

For Maori health support, please contact :

Name, position: Mark Brunton, Kaitakawaenga Rangahau Māori
(Facilitator Research Māori)
Telephone number: 03 479 8738
Email: mark.brunton@otago.ac.nz

You can also contact the health and disability ethics committee (HDEC) that approved this study on:

Phone: 0800 4 ETHICS
Email: hdecs@moh.govt.nz

This project has been reviewed and approved by the Southern Health and Disability Ethics Committee (Ref: 19/STH/197).

Consent Form

Please tick to indicate your consent to the following

I have read, or have had read to me, and I understand the Participant Information Sheet.		
I have been given sufficient time to consider whether or not to participate in this study.		
I have had the opportunity to use a legal representative, whanau/ family support, or a friend to help me ask questions and understand the study.		
I am satisfied with the answers I have been given regarding the study, and I have a copy of this consent form and information sheet.		
I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time without this affecting my medical care.		
I consent to the research staff collecting and processing my information, including information about my health.		
I understand the nature and size of the risks associated with the testing and treatment procedures, which are explained in the Information Sheet.		
I understand that my participation in this study is confidential and that no material, which could identify me personally, will be used in any reports on this study.		
I know that I will be given a petrol voucher (*a value of 50$*) as a reimbursement for the travel expenses associated with study participation.		
I understand the compensation provisions in case of injury during the study.		
I know whom to contact if I have any questions about the study in general.		
I understand my responsibilities as a study participant.		
I agree to my GP or other current provider being informed of my participation in this study. I agree for the researchers to contact my GP or other current provider if needed to determine my eligibility for participation in the study, and to be notified if any diagnosable condition is recorded.		
If I decide to withdraw from the study, I agree that the information collected about me up to the point when I withdraw may continue to be processed.	Yes ☐	No ☐
I wish to receive a summary of the results of the study.	Yes ☐	No ☐

Declaration by participant:

I hereby consent to take part in this study.

Participant's name:

Signature: Date:

Emergency contact person:

Please specify a contact person (a friend or a relative), in case of an emergency during the study participation. The contact details will be deleted from the file following your visit.

Name of a friend or relative:

Contact number:

Declaration by a member of the research team:

I have given a verbal explanation of the research project to the participant, and have answered the participant's questions about it.

I believe that the participant understands the study and has given informed consent to participate.

Researcher's name:

Signature: Date:
