Participant Information Sheet

Study title:	**Effect of Brain Blood Flow on Cognition Across Healthy Adulthood**		
Locality:	University of Otago	Ethics committee ref.:	18/CEN/142
Lead investigator:	Professor Jim Cotter	Contact phone number:	0273630894

You are invited to take part in a study on the effect of brain blood flow on cognition across the lifespan. 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 7 pages long, including the Consent Form. Please make sure you have read and understood all the pages.

WHAT IS THE PURPOSE OF THE STUDY?

It is well known that cognition (i.e., mental processing), particularly reaction time and memory, declines across the lifespan. With an aging population, it is not surprising that a decline in cognition can affect the individual, families, and communities alike. Scientists are curious as to why this occurs, and some argue it is because of a decline in brain blood flow. Determining the mechanisms behind the brain's aging is important for reasons such as developing strategies to combat this decline.
Thus, we want to know if and how age-related decreases in cognition are connected to an impairment in the function of the brain's blood vessels. To do this we invite you to participate in our randomised cross-over (between groups) study, funded by The School of Physical Education, Sport and Exercise Sciences. In addition to a familiarisation session, you will be asked to attend the lab on 2 occasions (each ~3.5 hours) and will be given either a placebo (sugar) pill, or ~100 mg of an anti-inflammatory medication. You will not know which pill has been allocated to which session.
The scientific background and the experimental protocols for this study have been internally reviewed by Division of Sciences, University of Otago, Scientific Peer Review Committee and the Health and Disability Ethics Committee (18/CEN/142).

WHAT WILL MY PARTICIPATION IN THE STUDY INVOLVE?

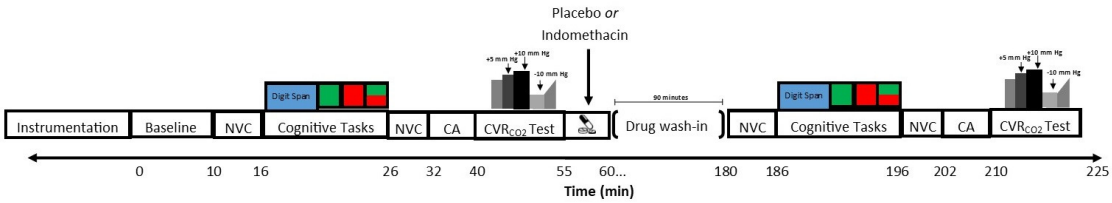
Prior to any testing, you will be asked to attend the lab for a "familiarisation session", where you will see the equipment and cognitive tests used on the days of testing. Here, we will ask

you to complete a questionnaire designed to test for cognitive impairment. We will also ask for your health history to determine if participation in this study is safe for you.

You will be asked to attend the lab for 2 additional testing sessions. Each session will take about 3.5 hours. After setting up the equipment, we will collect baseline data. Then, you will be asked to complete a cognitive battery (measuring reaction time and working memory) and 3 brain reactivity tests to changes in light, blood pressure, and CO_2.

1) *The cognitive battery* measures reaction time, accuracy, and short-term memory.
2) *Light reactivity tests (NVC)* involve cycles of eyes closed for 30 seconds, and eyes open (for 30 seconds) to a visual stimulus.
3) *Blood pressure reactivity tests (CA)* measure how quickly your blood pressure changes in response to standing from a seated position. This is done with cycles of 10 seconds sitting and standing, for a total of 3 minutes.
4) Lastly, the *CO_2 reactivity test* (CVR_{CO2}) involves breathing room air mixed with small amounts of CO_2. This will raise the blood levels of CO_2. Then, slight hyperventilation (fast breathing) will follow to decrease blood levels of CO_2.

After these tests, you will receive either a placebo (sugar) pill, or approximately 100 mg of Indomethacin. Indomethacin is an anti-inflammatory drug that works in similar ways to Ibuprofen. Then, after 90 minutes of rest (during which you are free to work, read, chat, or watch a movie), you will undergo a second administration of reaction time and working memory cognitive tasks, and brain reactivity tests (as mentioned above).
See the figure below for an illustrated timeline of testing sessions.



We ask that you do both sessions at the same time of day because of known time-of-day effects on cardiovascular control. You will also be instructed to eat the same meals/snacks on the days of testing, with no food consumption 2 hours prior to arrival. If you choose to participate, please drink an adequate volume of water and to refrain from caffeine, alcohol, and heavy exercise for 12 hours prior to each session.

What measurements are being taken?

Measures during these sessions will include:

- Blood pressure, using a finger cuff with live feedback a manual cuff your arm
- Heart rate, using an ECG that detects and records the frequency that your heart contracts.
- Respiratory gases, using a breath-through mask. The volume of air and concentrations of oxygen and CO_2 are used to determine how quickly you exchange these gases, and their levels in your blood. A small percentage of CO_2 will be added to inspired room air at certain points in each testing protocol. You will be informed when you are breathing additional CO_2.
- Brain blood flow velocity, using ultrasound probes secured on your temples with a headband, to measure blood flow in the largest arteries in your brain.
- Brain tissue oxygenation and blood volume, using a light called near infrared spectroscopy (NIRS), from a probe secured to your forehead.

- Cognitive function, using tasks that assess your executive functioning. These tasks include measures of response time, inhibition, and working memory.
- Perceptions, from verbal rating scales, to assess how you feel.

WHO CAN PARTICIPATE?

Eligibility Criteria

- Adults aged either 18 - 35, or 55 - 75 years old, with no signs of cognitive impairment;
- Non-smoker.

Exclusion Criteria:

- Allergic to or contraindication to taking NSAID
- Currently taking, or required to take any medication listed below:
    - Cardiac glycosides
    - Aminoglycosides
    - Diuretics
    - Anticoagulants
    - Antihypertensive
    - Aspirin
    - Non-steroidal anti-inflammatories
    - Corticosteroids
- Known cardiovascular, cerebrovascular, neurological, metabolic, respiratory, renal, or haematological disease or condition.

WHAT ARE THE POSSIBLE BENEFITS AND RISKS OF THIS STUDY?

Benefits potentially include:

- Learning aspects of your health and fitness. This includes your aerobic fitness, maximum heart rate, cognitive performance, blood pressure at rest, and your brain's blood flow function.
- Supporting novel research, important toward developments in brain health and aging.

Risks include:

- Ingesting Indomethacin: Some people experience stomach upset when taking one dose of Indomethacin. To minimise this risk, we will use the lowest effective dose possible (i.e., 1.2 mg/kg) and give you 50 mg of Simethicone (an anti-flatulence used previously to prevent indomethacin-related gastrointestinal upset). As Indomethacin decreases brain blood flow, there is a small risk of fainting upon changes in posture. However, our team is experienced in closely monitoring for pre-fainting cues.

  The possibility of choking on the pills is also relevant (i.e., as with any pill). We are using Indomethacin only acutely, but must also acknowledge that that long-term use (i.e., over 3 months) of drugs that block inflammatory processes may ultimately increase risk of cardiovascular disease, and other gastrointestinal and renal effects.

- Breathing Carbon Dioxide - When you breathe in gas mixtures containing carbon dioxide, you may slightly under-breathe, resulting in minor breathlessness and increased awareness of breathing. You will be carefully monitored for these symptoms and attempts will be made to remove any symptoms.

- Brain blood flow - Assessment with ultrasound is pain free. Ultrasound has the potential to cause adverse effects in experimental animals, but whether similar

effects also occur with humans in susceptible tissue (e.g., brain) in the doses used in experiments such as this requires further investigation. After more than a decade of ultrasound imaging in regional analgesia and in pain medicine interventions, there are no major reports of harm. The equipment that measures brain blood flow requires an adjustable head set to hold the probe in place. Some individuals find this uncomfortable over time. The researchers will alter the head set to maintain comfort for you throughout the trials.

WHO PAYS FOR THE STUDY?

Participation in this study involves a commitment of approximately 9 hours, including three visits to the School of Physical Education, Sport and Exercise Sciences. Upon completion of the study you will be reimbursed for any costs incurred with participation (e.g., transportation, food, parking etc). This occurs in the form of a $40 New World Voucher per testing session (i.e., up to a total of $80).

WHAT IF SOMETHING GOES WRONG?

If you were injured in this study, which is unlikely, you would be eligible for compensation from ACC just as you would be if you were injured in an accident at work or at home. 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 completely voluntary. This means that you have the choice to participate or withdraw at any time, with no disadvantage to you. If you choose to decline, you do not need to provide a reason. All information collected from you during this study will become confidential and made anonymous. However, you will be given full access to all this information. You will always be informed immediately if any adverse information about your health becomes available during testing. Upon completion of the study, if you would like to receive a copy of your results, or are interested in the final report, please email the primary investigator (e-mail supplied below).

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

All data obtained will be used solely for the purposes described above. However, these data may be made available for wider research in future, such as in performing a meta-analysis (i.e., a quantitative analysis that utilities all available studies on the effects of exercise mode or intensity on brain blood flow). If the data are used for such a purpose, they would be de-identified before being made available.
The data collected will be securely stored in such a way that only those mentioned below will be able to gain access to them (except for de-identified data as mentioned above). Data obtained as a result of the research will be retained for at least 5 years in secure storage. Please note that some personal information is necessary to be collected (including a fitness and medical questionnaire, weight/height/age, and personal contact details) as it serves purposes for group characterisation, screening, comparison, and contact. Your data will be assigned a personal identification number to ensure anonymity in both the analysis and documentation of results. The personal data will be accessible only by the researchers

named below and destroyed upon research completion. The results of the project may be reported in a scientific paper or conference, and a PhD thesis made available in the University of Otago Library (Dunedin), but your anonymity will be preserved. In any such reporting, the data included will not be linked to a specific participant.

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:

Ms Leena Shoemaker
Telephone: (027) 363 0894
leena.shoemaker@otago.ac.nz

Prof Jim Cotter
Telephone: (03) 479 9109
jim.cotter@otago.ac.nz

School of Physical Education, Sport and Exercise Sciences
55 Union St West, PO Box 56, Dunedin, 9054

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@hdc.org.nz

For Maori health support please contact :

Anne-Marie Jackson, Senior Lecturer
anne-marie.jackson@otago.ac.nz
Tel 64 3 479 8378

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

Consent Form

If you need an INTERPRETER, please tell us.

Please tick to indicate you consent to the following:

I have read, or have had read to me in my first language, and I understand the Participant Information Sheet.	Yes ☐	
I have been given sufficient time to consider whether or not to participate in this study.	Yes ☐	
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.	Yes ☐	
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.	Yes ☐	
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.	Yes ☐	
I consent to the research staff collecting and processing my information, including information about my health.	Yes ☐	
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 ☐	
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.	Yes ☐	
I understand the compensation provisions in case of injury during the study.	Yes ☐	
I know who to contact if I have any questions about the study in general.	Yes ☐	
I understand my responsibilities as a study participant.	Yes ☐	
I wish to be contacted about future research involvements.	Yes ☐	No ☐
I consent to researchers informing health practitioners with responsibility for my health care that I am taking part in this study.	Yes ☐	No ☐

Declaration by participant:
I hereby consent to take part in this study.

Participant's name:

Signature: Date:

Declaration by member of 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: