EXPLANATORY STATEMENT

Interaction between physical fitness and brain network plasticity induced by rTMS

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You are invited to take part in this study. Please read this Explanatory Statement in full before deciding whether or not to participate in this research. The purpose of this document is to outline the procedures involved in the study to allow you to make a full-informed decision as to whether you wish to take part. If you would like further information regarding any aspect of this project, you are encouraged to contact the
researchers via the phone numbers or email addresses listed above.

**Introduction**

Regular participation in aerobic exercise has been demonstrated to benefit cognition, stimulate plasticity of the brain, and prevent age-related cortical deterioration. Aerobic exercise has emerged as a successful and practical treatment approach for neuropsychiatric disorders and mental illnesses, such as depression, addiction and Alzheimer’s disease. We are interested in investigating whether TMS and aerobic exercise may have greater therapeutic effects used in conjunction, than when completed in isolation.

The aims of this study are three-fold i) to determine whether partaking in regular aerobic exercise results in detectable brain changes, ii) to establish effective TMS procedures that may inform future interventions and iii) to investigate whether physical fitness amplifies the efficacy of TMS.

**What will this study involve?**

**TMS:** Transcranial magnetic stimulation (TMS) is a non-invasive method for stimulating the outer layers of the brain in awake humans. TMS uses magnetic fields to generate small electric currents on the outer layer of the brain. A plastic coated coil is rested on the scalp above the cortical region to be stimulated. A brief electric pulse is passed through the coil, which generates a magnetic field that passes across the skull and generates an electric current in the underlying brain tissue. When TMS is delivered repetitively (rTMS) it can drive subtle changes in the brain that mimic the mechanisms involved in learning. These effects typically last for up to an hour after a single session of stimulation. Interestingly, a recent study has shown that multiple sessions of rTMS can induce long-lasting improvements in memory function, which persist for up to 15 days. rTMS is also used as a treatment for depression and is being investigated for other neurological conditions.

You will be asked to attend a total of 8 TMS sessions, held daily from Monday-Thursday over the course of two separate weeks, with a break of at least one-week in between. Each session of stimulation will run for approximately 25-30 minutes. The type of stimulation we will be using is called repetitive TMS (rTMS), which will involve short 2 s bursts of stimulation followed by 28 second breaks. Prior to commencing the TMS we will use a neuronavigation system to accurately position the TMS coil. 3D brain images obtained with MRI are used like a map to locate certain areas of your brain. We will use electromyography (EMG), which measures muscle activity in your hand via electrodes placed on the skin. We will stimulate two different regions of the brain. One week the TMS coil will be positioned over the left parietal cortex and the other week it will be positioned over the supplementary motor cortex.

**Behavioural assessments, fitness testing and brain scans:** In addition to the TMS stimulation you will be asked to complete:

- A VO2max aerobic fitness test at the beginning of the study. This test is a graded intensity fitness test conducted on a treadmill and will determine your current level of fitness. The protocol will last 8-18 minutes and continues until you reach your aerobic threshold. You will be asked to refrain from strenuous exercise for 24 hours prior to the test, to eat a good breakfast on the day of the test, and wear clothing appropriate for running.
- A 30-minute MRI scan at the beginning of the study to measure brain structure and function. This will help us determine the optimum position for TMS coil placement on the scalp. You will lie down on a table in the middle of a large, doughnut-shaped magnet. MRI uses magnetic fields to generate
3-D pictures of your brain. If you have previously participated in an MRI study at Monash Biomedical Imaging please let us know, as we may be able to use this data instead of performing another scan.

- Completion of questionnaires assessing general well-being and lifestyle and computerized behavioural tasks. These tasks will assess reaction times to stimuli presented on a computer screen and different types memory function. The questionnaires and behavioural assessments will take 45 minutes to complete and will be administered at five points (on Monday and Friday of each TMS stimulation week, and 2-weeks after completion of the TMS).

Physical activity monitoring: You will be asked to wear a Garmin fitness monitor during your participation in this study. This is a thin wristband that will record your day-to-day activity including steps, distance, calories expended, heart rate and sleep quality.

Am I eligible to participate?
You are eligible to participate if you are a healthy adult aged between 18 and 55, right-handed, and either physically active (at least 150 minutes deliberate exercise per week) or inactive (less than 60 minutes deliberate exercise per week). You will be capable of performing a short ~10-15 minute physical fitness test (as determined by a confidential physical activity readiness questionnaire). If you volunteer for this study, you will be asked to complete safety screening checklists and you may not be eligible to participate if you have contraindications to exercise, non-invasive brain stimulation, or magnetic resonance imaging (e.g. if you have a cardiac pacemaker, have experienced a head injury, have metal in your body, or experience seizures). Additionally, participants will also be screened for any history of intellectual disability, psychiatric or neurological illness, substance abuse disorder, past episodes of distress in enclosed spaces or diagnosis of claustrophobia and prescribed psychoactive medication.

Consenting to participate in the project and withdrawing from the research
Your participation in this study is completely voluntary and should you wish to withdraw at any stage, or to withdraw any unprocessed data you have supplied, you are free to do so without consequence. Your decision to withdraw will not affect the relationship between you and the researchers of this project or future projects conducted at Brain and Mental Health Laboratory or other research centres affiliated with this project. If you decide to withdraw, please notify a member of the research team.

Source of funding
This study has been funded by internal Monash University grants.

Possible benefits and risks to participants

Benefits
You will receive no direct benefit from this research. However, this research has the potential to directly inform current brain stimulation treatment practices by demonstrating methods which could improve TMS outcomes. For instance, TMS was recently approved as a method for treating depression in the US and Europe and there are now several private TMS clinics in Australia. This research will inform the development of new TMS-based therapies for chronic neurological and psychiatric illnesses.

Risks
Cognitive Testing: Some individuals may feel slightly tense when completing cognitive assessments such as those pertaining to memory function. You will not receive feedback on your performance, and any test scores will only be used to get a group-level impression of performance levels. You may feel tense or somewhat distressed in answering some of the screening questions, or in answering these questionnaires it may be apparent that you are currently experiencing distress. If this occurs, we can refer you to the appropriate Health and Wellbeing Services at Monash University (9905 3156), Headspace.
Brain imaging: Magnetic resonance imaging (MRI) is a non-invasive brain imaging procedure routinely used in human clinical and research contexts. There is currently no evidence that prolonged exposure causes any adverse health effects. Nonetheless, the scanning environment can elicit feelings of anxiety in some people, particularly if people feel claustrophobic in the enclosed space of the scanner. The MRI scanner will make loud hammering noises during some of the scan, we will therefore provide you with headphones or earplugs to lessen the noise. When in the scanner, you will be given a buzzer that can be used to alert staff to any discomfort or emergency. You should press the buzzer if you feel uncomfortable or if you want to withdraw participation. You are free to withdraw participation at any time.

The scans acquired are not for clinical purposes though a trained radiologist will inspect them for the presence of any incidental findings. In some cases, a previously unknown brain abnormality can be uncovered. Before your scan, you will be asked to indicate whether you wish to be informed about (i) all incidental findings; or (ii) only those adverse findings that would usually lead directly to treatment. You will also be asked whether you would like any incidental and/or adverse findings to be discussed with you by your usual General Practitioner (GP), another doctor of your choice, or by the MBI Radiologist. You are entitled to be informed of the results of the scan but we understand that you may not wish to receive the report yourself. Please see the attached incidental findings form for further information.

Brain stimulation: The main concern when using TMS is its potential to induce a seizure. This risk is very low, particularly in those who do not have a previous history of seizures (this has been estimated as being considerably lower than the seizure risk with commonly prescribed medications such as the anti-smoking medication Zyban). We will also minimise this risk by following safety guidelines that exist in the published literature (these limit the intensity, frequency and number of stimuli administered per session) and by excluding any participants with an elevated risk of seizure. Few seizures (<15 documented) have occurred since these guidelines were introduced over a decade ago (internationally many thousands of patients would have received TMS during this time). Monash Biomedical Imaging, where MRI and TMS will take place, has an established protocol for dealing with seizure-related emergencies. In the unlikely event that seizure does occur, an ambulance will be called immediately and researchers will apply first aid until emergency services are able to respond.

Repetitive TMS can also cause ringing in the ears or short-term hearing loss in some people. Earplugs will be made available to you.

TMS can also produce a tension type of headache through the stimulation of local scalp muscle contraction (~5% of subjects with high frequency stimulation in treatment studies). The incidence of this is dependent on the site of stimulation and especially the frequency. It is recommended that people who suffer from migraines or frequent/severe headaches do not participate in TMS studies. Additionally, some participants can feel faint or dizzy following TMS, usually those who also feel faint following medical procedures (e.g. giving blood). It is recommended that you do not participate if you have a history of fainting or feeling dizzy. If the stimulation feels uncomfortable during stimulation, please notify the researcher as small alterations can be made to minimise these sensations. Remember, you are free to withdraw at any time. If you develop a headache after stimulation, this can be treated with over the counter pain medication and will usually subside within 30 minutes. If you have any concerns about TMS, please contact Dr. Coxon or Dr. Rogasch.

Payment
Each participant who completes the study will be reimbursed $100 for their time. This payment will provide compensation for travel costs to the Monash Biomedical Imaging facility. It is not intended as a financial incentive, as participation is voluntary.

Confidentiality
For analysis purposes, your data will be assigned a unique numeric code and any identifying information will be removed. Any information obtained in connection with this project that can identify you will remain confidential and available to the research team only. It will only be disclosed with your permission, except as required by law. All identifying information will be stored in locked filing cabinets and password-protected computers on secure premises. The data will be stored for a minimum period of five years, consistent with legal requirements.

When the results of the research are published or presented at scientific conferences, no information will be included that reveals your identity without your prior permission. You are free to access your information at any time.

Sometimes, your data may be used to examine research questions that are not directly related to the study described in this document. In these cases, any data used will NOT have any information that can identify you. You can use the enclosed consent form to indicate whether you consent to your data being used for any additional purposes. Using the data in this way poses no additional risks to you.

You may also use the consent form to indicate whether you would like to be contacted to participate in other research conducted at our Centre.

Storage of data
Digital data from MRI will be stored and backed up on Monash Large Research Data Store (LaRDS). Digital data from EMG and working memory tasks will be stored on hard drive locked in a secured filing cabinet at MBI and backed up on LaRDS. Non-digital data such as consent forms, TMS safety screens etc. will be stored in a locked and secured filing cabinet at MBI. Data will be stored for a minimum of 7 years, after which time it will be destroyed.

Use of data for other purposes
Sometimes it is useful to use your data for research purposes other than those specified in this statement. For example, researchers may think of a new question that your data may help to address. You are free to consent to your data being used for these purposes on the enclosed Consent Form. If you do consent, your data will be completely de-identified and used for research purposes only. This use therefore poses no additional risks to you.

Results
Once the research is completed, a summary of the findings will be available to you if you wish to receive it. Individual results will not be provided. If you would like to be informed of the aggregate research finding, please contact Joshua Hendrikse on 0402910996 or via email at joshua.hendrikse@monash.edu

Complaints
Should you have any concerns or complaints about the conduct of the project, you are welcome to contact the Executive Officer, Monash University Human Research Ethics (MUHREC):

Executive Officer
Monash University Human Research Ethics Committee (MUHREC)
Room 111, Building 3e
Research Office
Thank you,

Mr Joshua Hendrikse
On behalf of this project’s research team