Plain Language Statement

Melbourne School of Psychological Sciences
Faculty of Medicine, Dentistry and Health Sciences

Project: Effect of Exercise and Brain Derived Neurotrophic Factor (BDNF) on Treatment Efficacy of Exposure Therapy in Posttraumatic Stress Disorder (PTSD)

Responsible Researcher: Professor Kim Felmingham

Other Researchers: Professor Barbara Rothbaum, Professor David Forbes, Professor Meaghan O'Donnell, Dr Simon Rosenbaum, Prof Richard Byrant, Dr. Katherine Chisholm, Dr Sean Cowlishaw, Dr Andrea Putica, Dr Kim Murray, Dr Winnie Lau, Ms Sevil Ince, Ms Hope O'Brien, , Ms Amanda Pearce, Mr Tim Dane Reynolds, Dr John Cooper, Ms Nicole Doyle, Ms Sophie Alexander, Ms Pascale Bockelmann, Ms Kirsteen Moss, Dr Rahul Khanna, Ms Sophie Yeung, Ms Clare McGinness, Dr Greg Roebuck, Ms Jenelle Baur, Professor Ben Harrison, Ms Holly Carey, Dr Trevor Steward, Dr Laura Finlayson-Short, Mr Oliver Eastwood, Mr Angus Burns

Primary contact: Ms Sophie Alexander, Tel: 8344 1155, Email: sophie.alexander1@unimelb.edu.au

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Introduction

Thank you for your interest in participating in this research project. The following few pages will provide you with further information about the project, so that you can decide if you would like to take part in. Please take the time to read this information carefully. You may ask questions about anything you don't understand or want to know more about. Your participation is voluntary. If you don't wish to take part, you don't have to. If you begin participating, you can also stop at any time.

What is this research about?

This research project is aiming to investigate whether combining aerobic exercise with exposure therapy to increase Brain derived neurotrophic factor enhance treatment response to exposure therapy with individuals who develop posttraumatic stress disorder (PTSD) after experiencing a traumatic event.

Following a traumatic event, most people experience emotional reactions such as feeling anxious and sad for a short period of time, and then over time these feelings reduce. However,

some people (about 30%) experience severe, ongoing emotional reactions that develop into emotional disorders such as PTSD.

Currently, Prolonged Exposure (PE) therapy is considered the gold-standard treatment for PTSD in which the aim is to reduce fear responses to trauma reminders. However, treatment effectiveness of PE is not at the desired level as some of those completing the treatment only show a partial response. This highlights a need to develop ways to improve our treatment response to PE. Evidence suggests that doing aerobic exercise increases a protein called Brain derived neurotrophic factor (BDNF) which has been associated with an improved capacity to regulate fear responses. Therefore, combining PE and exercise (to increase BDNF) has been suggested as a potential way to enhance the treatment response to PE. This study will investigate whether combining PE with aerobic exercise increases effectiveness of PE in treating PTSD after a traumatic experience.

This study is known as randomised controlled research. To find out whether combining exercise with PE increases the effectiveness of PE in treating PTSD, we need to compare PE combined with aerobic exercise to another condition where PE is received in the absence of aerobic exercise. We will do this by randomly allocating people into groups and giving one group PE with aerobic exercise and the other group PE with gentle stretching (and no exercise). This project is a blind study which means the trained clinician who will conduct the therapy don't know which group you are in. The study design is to ensure that researchers interpret the results in a fair and appropriate way, and avoids study researchers or participants jumping to conclusions.

What will I be asked to do?

When you called the BDNF research team to enquire about the project, you will have been given information about the Phoenix Traumatic Stress Research Clinic (Phoenix Clinic), and been given a Plain Language Statement outlining the intake process prior to providing verbal consent to engage in a 60 minute screening assessment, to identify whether you have developed PTSD following a traumatic event that you experienced and other mental health problems (such as depression) following a traumatic event that you experienced. You will also be asked physical health-related questions to identify whether you can engage in aerobic exercise safely.

If you have been invited and consent to participate in the BDNF study, you will initially complete an assessment session where your psychological and physical assessment will be made before the treatment. You will also provide a saliva sample which will be used to detect whether you carry a variant of a BDNF gene responsible from reduced levels of BDNF and has been associated with higher PTSD symptoms and poorer capacity to regulate fear.

Note: When the government restrictions are in place due to the impacts of COVID-19, participation in the BDNF study will be offered via Telehealth (videoconference) only. During this period psychological assessment will take place over videoconference only (supported by telephone if needed). Also, during this period instead of the physical assessment you will complete an exercise information session where the exercise/stretching component of the study will be explained to you, and your questions will be answered. In situations where government restrictions are eased or lifted, participation in the BDNF study will be offered via telehealth and/or via face to face appointments with appropriate COVID safe measures in place.

Then you will be randomly allocated to either the PE with aerobic exercise treatment group, or the PE with gentle stretching group. Both treatment conditions contain the PE treatment which has been shown as the most effective treatment for PTSD, they vary in whether you do exercise or stretching before each treatment session. Treatment will take place at Phoenix Traumatic Stress Research Clinic at the Royal Melbourne Hospital (Royal Park Campus). Once allocated, you will receive 10-weekly sessions of 90-minute face-to-face PE treatment, delivered by a trained clinician. Prior to each session you will be engaging in a 20 minute aerobic exercise (via cycling) or engaging in gentle stretching, depending on the group you have been allocated to.

Between the pre-treatment assessment week and first treatment week, you will complete a clinician assessment session where you will meet your therapist who will ask you some demographic questions, and questions about your mental health and will give you some information about the treatment. You will also engage in stretching or exercise for 20 minutes prior to the clinician assessment session. Each time you visit the clinic will take approximately two hours.

Note: Due to the impacts of COVID-19, when government restrictions are in place, the clinician assessment session, treatment sessions and exercise/stretching sessions will be delivered online. In situations where government restrictions are eased or lifted, these will be offered via telehealth and/or face to face appointments with appropriate COVID safe measures in place.

With your consent, 10% of your treatment sessions being audio recorded and reviewed by other clinicians working on the project to monitor and ensure that your sessions are conducted according to protocol. These recordings will then be deleted after they have been fidelity assessed. Brief details about PE are outlined below:

PE: Prolonged Exposure involves helping you to gradually address the difficult memories of your traumatic experience, as well as any situations you may be avoiding because of the traumatic experience. In a supportive and controlled fashion, PE involves: (a) learning about common reactions after a traumatic experience, (b) learning breathing relaxation to help manage anxiety, (c) creating a list of avoiding situations, (d) engaging in imaginal PE, which involves describing the traumatic event you experienced, with guidance and support from the trained clinician and (e) planning for ways to stay well in the future. PE also involves doing *in vivo* activities during the week, which involves confronting avoided situations in a gradual fashion. During each PE session your skin conductance will be measured, using two small non-invasive electrodes placed on your fingers which record the natural sweat gland activity in your fingers. This reflects the level of physical arousal you experience during each therapy session. Also throughout the study, you will be asked to wear an actigraphy watch (similar to a fitbit), this allows us to track exercise levels and sleep activity which may also impact on your ability to regulate fear.

Prior to the exercise and PE therapy sessions at week 2, 4 and 10 you will also complete a 20-minute experimental task where you will be asked to listen to a neutral recording and a recording of your trauma narrative while your heart rate, skin conductance and general mood state will be recorded. This task is designed to assess how different emotional responses may predict treatment outcome and help with identifying adjunct treatments for those who may not respond to frontline PTSD treatments. The task will be administered by a trained clinician working on the trial and is non-invasive.

Optionally you will be asked to provide blood samples before and after exercise or stretching before the PE session at week 3, 6 and 10. These blood samples will help us determine the

change in your BDNF levels during the exercise and aid our understanding of how exercise and BDNF increase effectiveness of PE treatment. If you are an antidepressant user, we will also measure your blood serotonin and nor-adrenaline levels since these have an effect on treatment effectiveness and on BDNF levels. You will not need to give another blood sample for these as we can assay them from the same blood we collected for the BDNF levels. Furthermore, during the course of treatment you will optionally provide one saliva sample before aerobic exercise or gentle stretching prior to the PE session at week 3, 6 and 10. This saliva sample will be used for hormonal analysis as certain hormones such as cortisol and estrogen have been suggested to affect fear learning and BDNF function. Bear in mind that provision of blood and saliva samples are optional therefore you can choose not to provide these samples. If you opt out of providing these samples, your enrolment in this trial and your treatment at the Phoenix Traumatic Stress Research Clinic will not be affected in any way.

Note: When government restrictions are in place due to COVID-19, you will not provide blood or saliva samples. In situations where government restrictions are eased or lifted, if you are receiving face-to-face treatment, the procedures outlined above will resume with appropriate COVID safe measures in place.

Psychological and Physical Assessments

Before beginning treatment, you will be given a set of questionnaires to complete at home assessing your level of PTSD symptoms, your mood, sleep quality, alcohol and substance use, quality of life, personality characteristics and your physical exercise habits. The questionnaires will take approximately 30-35 minutes to complete in total, and you will have the option to complete it in hardcopy, or via an online form. You will complete an assessment interview, during which you will be asked to answer some questions about your PTSD symptoms. The interview will take approximately 60-90 minutes to complete. You will also be asked further physical health related questions and your physical fitness level and exercise tolerance will be assessed in a 6-10 minute cycling test. If you are allocated to the PE+ aerobic exercise treatment group, the level of your individual physical fitness in this test will guide the level of aerobic exercise (cycling) you will be doing later on before each PE session.

After you have completed the treatment, we will contact you at certain time points to conduct telephone assessments and complete questionnaires (similar to those you were asked to complete before treatment) to assess any changes that may have occurred during treatment. Telephone assessments are conducted to identify the severity of your PTSD symptoms, and will take approximately 90 minutes to complete. They will occur after you complete treatment (i.e., after the 10-week period), and at a follow-up period of 6 months after treatment completion. As mentioned above, you will also be asked to complete a set of questionnaires which assess the level of psychological symptoms that you are experiencing, how you view these symptoms, and how you are managing them, as well as your current quality of life. The questionnaires will be sent to you by post or you can complete them online, and will take approximately 30 minutes to complete. These questionnaires will be completed at approximately the same time points as the telephone assessments.

The optional study sessions

Note: When government restrictions are in place due to COVID-19, all optional study sessions will be ceased until face-to-face operations can be resumed with government restrictions easing or being lifted. In situations where government restrictions are eased or lifted, if you are receiving face-to-face treatment, and consented to these sessions, the procedures outlined below regarding the optional study sessions will resume with appropriate COVID safe measures in place.

We would also like to invite you to participate in extra experimental sessions where we will investigate the effect of aerobic exercise and increases in BDNF on the capacity to regulate fear responses in an experimental task. Evidence suggests that the inhibition of fear responses in this experimental task are predictive of the development of PTSD and PE therapy success. Therefore, data from these sessions will inform our understanding of underlying mechanisms involved in PE treatment of PTSD, and the effect of exercise and BDNF change on these mechanisms, which will help us find ways to increase the effectiveness of PE. These sessions are optional and you can participate in the study without participating in these optional sessions. These sessions will take place at the School of Psychological Sciences, The University of Melbourne Parkville Campus. Choosing not to engage in these additional study sessions will not affect your treatment in this trial or at the Phoenix Treatment Research Centre in any way.

If you opt to participate in these study sessions, you will be asked to attend to the clinic for 3 separate sessions of approximately one hour duration. These sessions will take place after the PE session 2, session 6 and session 10 (on a different day during the week of these sessions). In these sessions depending on the group you have been allocated to, you will either engage in aerobic exercise or gentle stretching for 20 minutes. Also, you will complete an experimental task where you will be looking at different coloured circles. Whilst watching these circles, you will occasionally receive a mild electric stimulus that is uncomfortable but not painful. The level of this mild electrical stimulus will be chosen by you. You will have your arousal level recorded during this task by small electrodes placed on your fingertips that measure your sweat gland activity. This task will take approximately 30 minutes to complete and has been safely used in many studies.

As part of this task, you will also provide 2 blood samples; one before and one immediately after the exercise or stretching and 2 saliva samples; one before the exercise or stretching and one after the experimental task. Blood samples will reveal any changes in BDNF levels before and after the exercise/stretching, while saliva samples will be used for hormonal analysis (cortisol and estrogen).

You will be paid 50$ for your participation in each of these optional sessions (a total of $150 across the therapy trial)

What are the possible benefits?

We cannot guarantee that you will receive any benefits from this research. However, PE is one of the most effective treatments available for PTSD. As such, possible benefits may include improvement in symptoms of PTSD. Furthermore, aerobic exercise or gentle stretching in itself has physical health benefits.

You will be reimbursed with a $25 Coles/Myer voucher after you have completed the 6-month follow-up assessment.

If you participate in optional experimental sessions, you will be paid 50$ for each session.

Potential benefits of the research for the wider community include improving the effectiveness of psychological treatments for PTSD. Specifically, this research will contribute toward improved understanding of treatment response to PE in PTSD and may inform novel non-pharmacological, exercise based interventions to improve patient outcomes.

What are the possible risks?

There are few risks associated with involvement in this project. However, it is important to note that all effective psychological interventions have the potential to cause distress to some degree – as this is part of the process of "working through" the traumatic experience. The prospect of confronting your memory of the traumatic event during PE treatment especially may seem frightening to you, however you will learn skills to manage distress, and any distress you experience will reduce during the sessions. While no evidence suggests that the psychological treatments being offered are detrimental, your therapist in the trial will provide appropriate support in the event that you become upset or experience any distress (or unusual) symptoms.

Some participants may feel physical distress during aerobic exercise if allocated to the PE+ aerobic exercise condition. However the intensity of the exercise will be pre-determined individually for each person based on their physical fitness, and their physical tolerance of the exercise will be monitored by researchers throughout the exercise. You will be able to stop the exercise if you feel very distressed. Furthermore, some participants may feel embarrassed to provide saliva samples in front of the researcher, therefore you will have the option to provide these without the researcher being present.

We will be drawing blood from participants who agree to provide blood samples. If you opt into for this, you may experience mild physical discomfort in your arm while providing blood samples. The blood draws will be collected by a trained researcher who also is a trained nurse, in a comfortable, private setting following best-practice protocol.

Note: If you are participating in the trial via telehealth, we will not be able assess your individual fitness level to adjust the intensity of the exercise you may receive should you be allocated to the aerobic exercise group. We will use other measures to adjust the intensity of your exercise if you are in the exercise group and deliver the exercise online with a trial member guiding you throughout the exercise via videoconferencing. It is still possible you may feel physical distress during the exercise. If this occurs, we will ask you to stop the exercise. Also, you can stop the exercise or any other component of the study whenever you want.

<u>Additionally, if you are doing the optional extra sessions;</u>

Some participants may feel a mild level of discomfort or anxiety in receiving the mild electrical stimulus as part of the experimental task. However, the level of the electrical stimulus is pre-determined by you, in a level it is uncomfortable but not painful.

A researcher will be monitoring your distress levels throughout each element of the study and will give you a telephone follow-up if you felt distressed during or after the session.
You may stop or withdraw from the study at any time without penalty.

Can I have other treatments during this project?

If you participate in this study, you cannot receive any other psychological treatments (apart from supportive counselling). You may continue to take antidepressants and other medications during this study, apart from the Beta Blockers (due to their effect on heart rate which we will use to determine the your physical fitness and intensity of your exercise).

Are there alternatives to participation?

Before participating in this project, you may discuss options such as psychological interventions or medications with a healthcare worker (for example, a hospital doctor or your GP). In many cases, the intervention offered in this study will be similar to that you would receive from a private psychologist. You will also be asked if you would like to be contacted about other trials and studies at Phoenix Australia and the University of Melbourne that may be relevant to you in the future.

Do I have to take part?

No. Participation is completely voluntary. You are able to withdraw at any time. If you decide to withdraw, please notify a member of the research team. After you withdraw, your personal and health information collected through the study will be kept to ensure the results of the research can be measured properly. If you do not want your personal and health information to be kept for the study's purposes, please tell a member of the research team once you withdraw.

Will I hear about the results of this project?

Results of this project will be published and presented in a variety of forums including reports, media, peer review publications, and other public forums. A brief report containing a summary of the project's findings will be uploaded to the Phoenix Clinic's website for you to access when the study has finished. Also, you will have the option of having the link of this summary report to be emailed to you.

What will happen to information about me?

Any information about your identity will remain confidential, and all data will remain **de-identified** which means we remove your name and other identifying information from your data and replace with a subject code**.** We plan to publish the results from the study in scientific journals. All published information will be group data only, therefore individual information will not be identified. It is possible that we may use the data collected in this study for future research with similar aims to improve the mental health of people impacted by traumatic experiences. In consenting to this study, you are also giving consent for us to use your data for future research which would be subject to approval from a Human Research Ethics Committee.

Only the researcher team will have access to your personal information. All hardcopies of your individual data will be stored in locked cabinets at Phoenix Australia (and at the Melbourne School of Psychological Sciences if you opt in for the experimental sessions) will be scanned and stored electronically, and hard copies will be securely destroyed. The database containing all de-identified information will be stored in a locked room at Phoenix Australia (and at the Melbourne School of Psychological Sciences if you opt in for the experimental sessions). The computer will be secured by password access. The audio recordings of your verbal consent provided for telephone screening purposes will be stored on a password protected computer in

a locked room at Phoenix Australia, with access restricted to the research team only. The audio recordings of assessment and treatment sessions will be stored on a password protected computer in a locked room at Phoenix Australia with access restricted to your clinician and the clinician from within the project team who is rating them. These recordings are optional and you are asked for your consent for this on the consent form. Electronic copies of data gathered during this study will be securely disposed of 7 years after the publication of this study or any future studies using this data. The audio recordings of assessments and therapy will be deleted after they have been fidelity assessed.

The saliva and blood samples you give will be collected and stored under a de-identified unique code given to each participant. Both saliva and blood samples will be stored in locked freezer rooms at the Melbourne School of Psychological Sciences until they are sent for analyses under ID codes only. After the analyses, your saliva and blood samples will be disposed of.

You will have the option to give us the consent for your genetic data to be used for future as-yet unspecified research (in the event that future genotypes may be uncovered in research which are relevant for fear extinction or memory).

As you will be receiving psychological treatment in this study, it will be important that your local doctor be advised of your involvement in this research project. We will send a letter to your GP to notify them of your involvement if you provide consent for us to do so.

How can I access my information?

In accordance with relevant Australian and/or Victorian privacy and other relevant laws, you have the right to access the information collected and stored by the researchers about you. You also have the right to request that any information, with which you disagree, be corrected. Please contact one of the researchers named at the end of this document if you would like to access your information.

What happens if I am injured as a result of participating in this project?

If you suffer an injury as a result of your participation in this research project, please contact the research staff. Hospital care and treatment will be provided by the public health care system (Medicare) at no cost to you if you are eligible for Medicare benefits and elect to be treated as a public patient.

Who is funding this project?

This project has been funded by the National Health and Medical Research Council of Australia (NHMRC).

Where can I get further information?

If you would like more information about the project, please contact Juhi Khatri on 8344 5170.

Who can I contact if I have any concerns about the project?

This research project has been approved by the Human Research Ethics Committee of The University of Melbourne. If you have any concerns or complaints about the conduct of this research project, which you do not wish to discuss with the research team, you should contact the Manager, Human Research Ethics, Research Ethics and Integrity, University of Melbourne, VIC 3010. Tel: +61 3 8344 2073 or Email: HumanEthics-complaints@unimelb.edu.au. All complaints will be treated confidentially. In any correspondence please provide the name of the research team or the name or ethics ID number of the research project.