Participant Information Sheet/Consent Form

Interventional Study - *Adult providing own consent*

Monash Alfred Psychiatry Research Centre (MAPrc); School of Psychology, Deakin University; Monash Biomedical Imaging, Monash University

Title	*Theta burst stimulation (TBS) to improve social relating in autism spectrum disorder (ASD)*
Project Number	*432/16*
Short Title	*TBS-ASD*
Project Sponsor	*Deakin University*
Principal Investigators	*A/Prof. Peter Enticott, Prof. Paul Fitzgerald*
Associate Investigators	*Dr. Melissa Kirkovski, Dr. Bernadette Fitzgibbon, Dr. Natalia Albein-Urios, A/Prof. Kate Hoy, Ms. Susan McQueen, Dr. David Elliot, Ms. Lenore Wambeek*

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in this research project. This is because you have been diagnosed with autism spectrum disorder (ASD). The research project is testing a new treatment for ASD. The new treatment is called “theta burst stimulation” (TBS), which is a form of repetitive transcranial magnetic stimulation (rTMS).

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don’t understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this research is voluntary. If you don’t wish to take part, you don’t have to.
If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

- Understand what you have read
- Consent to take part in the research project
- Consent to have the tests and treatments that are described
- Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

2 What is the purpose of this research?

Many individuals with ASD experience difficulty with social functioning; for example, in understanding what other people are thinking or feeling. This may cause significant distress, or lead to difficulties and anxiety in social situations. There are very few treatment options for improving abilities related to social functioning in ASD. The aim of this project is to determine whether TBS can be used to improve social function, and to investigate associated changes in brain activity. As noted, TBS is a form of rTMS. rTMS is a safe and non-invasive means of stimulating nerve cells in a particular part of the brain via the administration of a brief magnetic pulse. We have previously found that rTMS can benefit social aspects of ASD.

In this study we will stimulate regions of the brain that are involved is social understanding and social communication. These regions are (1) dorsomedial prefrontal cortex (dmPFC) and (2) right temporoparietal junction (rTPJ). All participants will undergo stimulation of both brain regions, but at different times (6-months apart). The use of TBS is considered preferable to "standard" rTMS because it is a very short treatment (3 minutes per treatment) and is typically tolerated very well.

20 people (aged 14-30 years) will take part in the study, which is being conducted at three places: Monash Alfred Psychiatry Research Centre (MAPrc, St Kilda Rd, Melbourne), Deakin University (Burwood Highway, Burwood), and Monash Biomedical Imaging (MBI, Blackburn Rd, Clayton). Participants will be recruited from around Australia, but primarily the greater Melbourne area.

TBS is an experimental treatment. This means that it is not an approved treatment for ASD in Australia or elsewhere.

This research has been initiated by the study investigator, A/Prof. Peter Enticott. This research has been funded by the Brain and Behaviour Research Foundation (New York, USA).

3 What does participation in this research involve?

If you decide to take part in this project, you will be asked to take part in a number of interviews and procedures. Firstly, we will ask you some questions about your health. These questions will be asked to determine whether you are eligible to take part in the study. We will also ask you to provide a letter or report confirming your diagnosis of ASD; if you are not able to provide this, we will seek permission (via the consent form) to contact your doctor or psychologist directly to confirm your diagnosis.

We will then ask some questions about yourself that are relevant to ASD. This will include, for example, what you enjoy doing and how much you like being with other people. We will also ask you to have someone who knows you well (i.e., a parent or spouse) to complete a questionnaire. You can nominate this person, and we will give you some information to give to them; we will ask that they agree to complete this questionnaire another 8 times during the study.

We will then ask you to complete some cognitive tasks on a computer. These tasks generally test how well you can guess what other people are thinking or feeling by the way they behave. You can complete these (and other) assessments at either the Monash Alfred Psychiatry Research Centre (St Kilda Rd, Melbourne) or Deakin University (Burwood Highway, Burwood).

You will then undergo a magnetic resonance imaging (MRI) brain scan at Monash Biomedical Imaging (Clayton). The MRI brain scan takes 30 minutes, during which you will be asked to lie still in an MRI scanner. (Please note that with preparation time for you attend the MRI facility for up to one hour.) You will perform a simple task in the MRI, which involves watching simple animations and answering questions about these animations. MRI is a routinely performed,

painless ways of examining brain structure and activity. We will use the MRI to assist in our understanding of brain's response to TBS. This may help us better understand how the treatment works and to determine who is likely to respond to treatment and why.

After taking part in the interview and tasks, we will administer transcranial magnetic stimulation (TMS) to the area of the brain that controls the muscles in your hand. This will measure how excitable your brain is, and is used to help us determine the personalised settings that will be used for your TBS treatment. This takes approximately 10 minutes and is not uncomfortable, although you may feel some twitches in the muscle of your hand while the TMS is occurring.

All people in the trial will be treated with two courses of TBS treatment. Each course involves treatment each weekday for four weeks. There will be approximately 6-months between each course of treatment. They will be identical except for the brain region stimulated; in one course the dmPFC will be stimulated, while in the other course the rTPJ will be stimulated. The order in which you receive these will be determined randomly, and the staff member completing your assessments will not know the order of treatments. During each treatment course, you will be asked to attend the Monash Alfred Psychiatry Research Centre each weekday (Monday to Friday) for 3 minutes of TBS treatment. Including setup time, you should only be in treatment for 5-10 minutes. At the end of each of the treatment weeks, we will ask you to complete some thinking and memory tasks on a computer (approximately 30-45 minutes).

Following each of the 4-week treatment courses, we will again ask you some questions about yourself that are relevant to ASD, and to complete the cognitive tasks on a computer. At this point you will also undergo another MRI scan. We will then meet with you again one month later to repeat these questions and cognitive tasks. You will be asked to come in to undergo the assessment another two times (once 3 months after the last rTMS treatment, once 6 months after the last rTMS treatment). You will then undergo another MRI scan, and a 4-week treatment course to the other brain region. Again, we will ask you to complete some thinking and memory tasks on a computer at the end of each treatment week. We will also ask you to complete an MRI scan after your second treatment course, and to repeat the questions and cognitive tasks at the same timepoints as those listed above (after treatment, 1-month, 3-months, and 6-months).

During each TBS session you will be awake, alert and aware of what is happening at all times. During TBS a coil will be placed against the head through which TBS is administered. This is connected to a machine that sends an electrical current through the coil. The current produces a magnetic field that is very focused and is able to stimulate electrical activity in nerves below the coil. These are usually nerve cells in the outer layers of the brain. The sensation associated with TBS are mild, and most people describe it as a tapping sensation on their head. During a TBS procedure, you will hear clicking sounds as the current passes through the coil. You will wear earplugs so this noise doesn't disturb you.

You will not be paid for your participation in this research, but you will be reimbursed $120 to contribute towards costs that you incur as a result of participating in this research project (e.g., travel). If you complete only part of the study and then decided to withdraw, you will be reimbursed a proportion of this amount based on the proportion of the study completed.

Please note that no study procedures will be performed until consent has been obtained.

4 What do I have to do?

You will be able to continue taking your usual medication if you participate in this study, but you will need to inform us of any changes to this medication that occur during your participation in the study.

There are several reasons why you may not be able to take part in this study. These include:

- The presence of metal anywhere in the head (except the mouth)

- A history of seizure or epilepsy
- A history of serious head injury
- The presence of certain implanted medical devices (e.g., cardiac pacemaker, medication pumps)
- Serious heart disease (as there is an increased risk of serious injury in the event of a seizure)
- Employment as a professional driver or machine operator (as the event of a seizure may affect employment)
- Pregnancy (female participants will be required to undergo a urine screen)
- Certain neurological or psychiatric diagnoses
- A measured intelligence quotient of less than 55

5 Other relevant information about the research project

There will be 20 participants in this study, all of whom are taking part at the Monash Alfred Psychiatry Research Centre (with the option of completing assessments at either Monash Alfred Psychiatry Research Centre or Deakin University) and Monash Biomedical Imaging. This is a follow-on study from our previous trials of rTMS in ASD, which have been conducted at the Monash Alfred Psychiatry Research Centre.

6 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with The Alfred, Monash University, or Deakin University.

7 What are the possible benefits of taking part?

We cannot guarantee or promise that you will receive any benefits from this research; however, possible benefits may include an improvement in social understanding and functioning, including an increased ability to accurately infer what other people are thinking or feeling.

8 What are the possible risks and disadvantages of taking part?

Theta Burst Stimulation (TBS)

Medical treatments often cause side effects. You may have none, some or all of the effects listed below, and they may be mild, moderate or severe. If you have any of these side effects, or are worried about them, talk with your study doctor. Your study doctor will also be looking out for side effects.

There may be side effects that the researchers do not expect or do not know about and that may be serious. Tell your study doctor immediately about any new or unusual symptoms that you get.

Many side effects go away shortly after treatment ends. However, sometimes side effects can be serious, long lasting or permanent. If a severe side effect or reaction occurs, your study doctor may need to stop your treatment. Your study doctor will discuss the best way of managing any side effects with you.

There are several potential side effects that might be experienced during a TBS procedure.

Noise: The clicking noise made by the coil may be uncomfortable. You will wear earplugs during treatment to minimise any discomfort.

Headache: A headache can occur during TBS, and is thought to affect approximately 3% of participants. It is thought to be caused by stimulation of nerves in the scalp. If you were to experience such a headache, it will respond quickly to simple pain medication such as aspirin or paracetamol.

Scalp Sensation: During the treatment itself, you might feel a tapping or twitching sensation on your scalp as the magnetic pulse stimulates muscles in your scalp as it passes into the brain. This sensation varies between people from very soft to quite strong. If you find it uncomfortable, we will use a lower stimulation intensity and only increase it as you find it tolerable.

Seizure: The main concern associated with rTMS (which includes TBS) is its potential to induce a fit or seizure. This risk is extremely low, but is increased for those with a history of seizure activity (where a seizure resulting from rTMS affects about 2% or 2 in 100 of such individuals). If you have ever experienced a seizure you will not be able to take part in this study. Investigators using rTMS have developed safety guidelines to minimise the risk of seizure. The TBS we provide is well within what is considered to be safe. It is important to note that experiencing a seizure induced by rTMS has never led to the development of epilepsy or increased the probability of having subsequent unprovoked seizures. There will always be medically trained staff available when you have TBS. Staff will monitor you and know how to treat a seizure should one occur.

The effects of TBS on the unborn child and on the newborn baby are not known. Because of this, it is important that research project participants are not pregnant or breast-feeding and do not become pregnant during the course of the research project. You must not participate in the research if you are pregnant or trying to become pregnant, or breast-feeding. If you are female and child-bearing is a possibility, you will be required to undergo a pregnancy test prior to commencing the research project. This test will be processed by a female member of the nursing staff.

If you do become pregnant whilst participating in the research project, you should advise your study doctor immediately. Your study doctor will withdraw you from the research project and advise on further medical attention should this be necessary. You must not continue in the research if you become pregnant.

Your ability to drive or use public transport will not be impaired following TBS.

It is also possible that there are unknown risks of TBS.

Magnetic Resonance Imaging (MRI)

There are no known risks associated with having an MRI scan, unless you have metal implanted in your body (e.g., a pacemaker, surgical staples or bone plates). This does not include dental fillings. Bringing metal into the scanner can be dangerous because of the very strong magnetic field. If you have any metal implants you will not be able to participate. Prior to going into the MRI scanner, you will be screened by research staff and the MRI technologist to make sure that you can safely be put into the scanner. There is no harmful radiation and no need for injections with MRI scanning.

The MRI scanner is shaped like a narrow tunnel. Foam cushioning and Velcro straps are used to keep your head relatively still during scanning. While the mask, cushions and straps are restraining, they should not be uncomfortable. Some people may experience claustrophobia while having an MRI scan. Please let us know if you have experienced claustrophobia in the

past. The MRI scanner is noisy, so you will wear ear plugs and headphones to reduce the noise. We will be able to see you and communicate with you during the scanning, and you will be able to stop the machine at any time by pushing a button. If you are becoming uncomfortable or having difficulty concentrating during the session, we can pause or stop the scanning.

As part of this research study we will obtain a limited number of pictures of your brain. Minor changes are sometimes found in completely healthy people. If any abnormal findings are present in your scan, the Principal Investigators will discuss these with you and what these findings may mean. Because these images are taken only for research purposes abnormalities that might be detectable by clinical (i.e., non-research) MRI scans are not always seen. It is possible, however, that the MRI may uncover a significant abnormality, in which case you would be notified and referred for further clinical evaluation. There may be wider implications from abnormal findings (e.g., for future applications for some kinds of insurance).

Other

We will ask you if you have used illegal drugs. That information will be stored in a re-identifiable (or coded) format. In the event that the researchers are required to disclose that information, it may be used against you in legal proceedings or otherwise.

9 What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the research project. If you decide to withdraw, your study doctor will make arrangements for your regular health care to continue. If you decide to continue in the research project you will be asked to sign an updated consent form.

Also, on receiving new information, the Principal Investigators might consider it to be in your best interests to withdraw you from the research project. If this happens, they will explain the reasons and arrange for your regular health care to continue.

10 Can I have other treatments during this research project?

Whilst you are participating in this research project, you can continue to take the medications or treatments you have been taking for your condition or for other reasons. It is important to tell the study staff about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell the study staff about any changes to these during your participation in the research project.

11 What if I withdraw from this research project?

If you decide to withdraw from the project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing.

If you do withdraw your consent during the research project, the study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected by the researchers up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell them before you join the research project.

12 Could this research project be stopped unexpectedly?

This research project may be stopped unexpectedly for a variety of reasons. These may include reasons such as:

- Unacceptable side effects
- The treatment being shown not to be effective
- The treatment being shown to work and not need further testing
- Decisions made by local regulatory/health authorities

13 What happens when the research project ends?

You will be sent a summary of the main findings when the project has been completed.

Please note that TBS will not be available after completing the study.

Part 2 How is the research project being conducted?

14 What will happen to information about me?

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential. Your information will be used for the purpose of this research project or for another purpose by the researcher (for which ethical approval will be sought). Your information will only be disclosed with your permission, except as required by law. All personal information that can identify you will be stored at MAPrc in a locked area by the investigators and will be kept under safe storage indefinitely as per the hospital protocol. Electronic data will be kept on a secure server hosted by Deakin University. All tests results will be labelled with a numerical code and will not contain any information that can identify you as a participant. Only the researchers A/Prof. Enticott, Prof. Fitzgerald, and Dr. Kirkovski will have access to the data.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission.

Information about your participation in this research project may be recorded in your health records.

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

Any information obtained for the purpose of this research project that can identify you will be treated as confidential and securely stored. It will be disclosed only with your permission, or as required by law.

15 Injury

If you suffer any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

16 Who is organising and funding the research?

This research project is being conducted by A/Prof. Peter Enticott and Prof. Paul Fitzgerald. It is funded through a NARSAD Independent Investigator Award to A/Prof. Peter Enticott from the Brain and Behaviour Research Foundation.

No member of the research team will receive a personal financial benefit from your involvement in this research project (other than their ordinary wages).

17 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HRECs of The Alfred, Deakin University, and Monash University.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

18 Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the principal study doctor on (03) 9076 6564 or any of the following people:

Clinical Contact Person

Name	Prof. Paul Fitzgerald
Position	Professor of Psychiatry
Telephone	(03) 9076 6564 (business hours) or (03) 9076 2000 (after hours)
Email	paul.fitzgerald@monash.edu

Study Contact Person

Name	A/Prof. Peter Enticott
Position	Associate Professor of Psychology (Cognitive Neuroscience)
Telephone	(03) 9244 5504
Email	peter.enticott@deakin.edu.au

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC name	Alfred Hospital Ethics Committee
Telephone	(03) 9076 3619
Email	research@alfred.org.au

Consent Form - *Adult providing own consent*

Title	*Theta burst stimulation (TBS) to improve social relating in autism spectrum disorder (ASD)*
Project Number	*432/16*
Short Title	*TBS-ASD*
Project Sponsor	*Deakin University*
Principal Investigators	*A/Prof. Peter Enticott, Prof. Paul Fitzgerald*
Associate Investigators	*Dr. Melissa Kirkovski, Dr. Bernadette Fitzgibbon, Dr. Natalia Albein-Urios, A/Prof. Kate Hoy, Ms. Susan McQueen, Dr. David Elliot, Ms. Lenore Wambeek*

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand. I understand the purposes, procedures and risks of the research described in the project.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to The Alfred, Monash University, and Deakin University concerning my disease and treatment for the purposes of this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received. I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care. I understand that I will be given a signed copy of this document to keep.

☐ I consent for the data collected in this project to be used for another purpose by the researchers (for which ethical approval will be sought). (Please tick if you agree.)

Name of Participant (please print) _____

Signature _____ Date _____

Name of Witness* to Participant's Signature (please print) _____

Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/ Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

Form for Withdrawal of Participation - *Adult providing own consent*

Title	*Theta burst stimulation (TBS) to improve social relating in autism spectrum disorder (ASD)*
Project Number	*432/16*
Short Title	*TBS-ASD*
Project Sponsor	*Deakin University*
Principal Investigators	*A/Prof. Peter Enticott, Prof. Paul Fitzgerald*
Associate Investigators	*Dr. Melissa Kirkovski, Dr. Bernadette Fitzgibbon, Dr. Natalia Albein-Urios, A/Prof. Kate Hoy, Ms. Susan McQueen, Dr. David Elliot, Ms. Lenore Wambeek*

Declaration by Participant

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with The Alfred, Monash University, or Deakin University.

Name of Participant (please print) _____

Signature _____ Date _____

Relevant Circumstances (to be completed by Senior Researcher):

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of and information concerning withdrawal from the research project.

Note: All parties signing the consent section must date their own signature.