BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-046830
Article Type:	Protocol
Date Submitted by the Author:	11-Nov-2020
Complete List of Authors:	Enticott, Peter; Deakin University School of Psychology Barlow, Karen; The University of Queensland Child Health Research Centre, Child Health Research Centre; Children's Health Queensland Hospital and Health Service Hickie, Ian; The University of Sydney Brain and Mind Centre, Brain and Mind Centre Licari, Melissa; Telethon Kids Institute Rogasch, Nigel; The University of Adelaide Adelaide Medical School; South Australian Health and Medical Research Institute Middeldorp, Christel; The University of Queensland Child Health Research Centre; Children's Health Queensland Hospital and Health Service Clark, Scott; The University of Adelaide Adelaide Medical School Vallence, Ann-Maree; Murdoch University, School of Psychology and Exercise Sciences; Murdoch University, Centre for Molecular Medicine and Innovative Therapeutics Boulton, Kelsie; The University of Sydney Brain and Mind Centre Guastella, Adam; The University of Sydney Brain and Mind Centre, Clinical Research Unit Whitehouse, Andrew; Telethon Kids Institute; Cooperative Research Centre for Living With Autism Galletly, Cherrie; The University of Adelaide Adelaide Medical School Alvares, Gail; Telethon Kids Institute Fujiyama, Hakuei; Murdoch University, School of Psychology and Exercise Sciences Heussler, Helen; The University of Queensland Child Health Research Centre, Child Development; Children's Health Queensland Hospital and Health Service, Centre fro Children's Health Research Craig, Jeffrey; Deakin University School of Medicine, School of Psychology Kirkovski, Melissa; Deakin University School of Psychology Mills, Natalie; The University of Adelaide Adelaide Medical School Rinehart, Nicole; Deakin University School of Psychology Donaldson, Peter; Deakin University School of Psychology Ford, Talitha; Deakin University School of Psychology Caeyenberghs, Karen; Deakin University School of Psychology, School of Psychology Albein-Urios, Natalia; Deakin University School of Psychology, School of Psychology Bekkali, Soukayna; Deakin University School of Psychology

	Fitzgerald , Paul; Monash University Central Clinical School; Epworth HealthCare, Epworth Centre for Innovation in Mental Health
Keywords:	Child & adolescent psychiatry < PSYCHIATRY, Developmental neurology & neurodisability < PAEDIATRICS, Paediatric neurology < PAEDIATRICS, Neurophysiology < NEUROLOGY

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Repetitive transcranial magnetic stimulation (rTMS) in autism spectrum disorder: protocol for a multicentre randomised controlled clinical trial

Peter G. Enticott*, School of Psychology, Deakin University, Geelong, Australia
Karen Barlow, Child Health Research Centre, The University of Queensland, South Brisbane, Australia; Children's Health Queensland Hospital and Health Service, Herston, Queensland
Ian Hickie, Brain and Mind Centre, University of Sydney, Camperdown, Australia
Melissa K. Licari, Research Fellow, Telethon Kids Institute, The University of Western Australia, Nedlands, Australia
Nigel C. Rogasch, Adelaide Medical School, The University of Adelaide, Adelaide, Australia; South Australian Health and Medical Research Institute (SAHMRI), Adelaide, Australia
Christel M Middeldorp, Child Health Research Centre, The University of Queensland, South Brisbane, Australia; Children's Health Queensland Hospital and Health Service, Herston, Queensland
Scott Clark, Adelaide Medical School, The University of Adelaide, Adelaide, Australia
Ann-Maree Vallence, School of Psychology and Exercise Sciences, Murdoch University, Murdoch, Australia; Centre for Molecular Medicine and Innovative Therapeutics, Murdoch University, Australia
Kelsie A. Boulton, Brain and Mind Centre, University of Sydney, Camperdown, Australia
Adam Guastella, Brain and Mind Centre, University of Sydney, Camperdown, Australia
Andrew J. O. Whitehouse, Telethon Kids Institute, The University of Western Australia, Nedlands, Australia; Cooperative Research Centre for Living with Autism, St Lucia, Queensland, Australia
Cherrie Galletly, Adelaide Medical School, The University of Adelaide, Adelaide, Australia
Gail Alvares, Telethon Kids Institute, The University of Western Australia, Nedlands, Australia
Hakuei Fujiyama, School of Psychology and Exercise Sciences, Murdoch University, Murdoch, Australia
Helen Heussler, Child Health Research Centre, The University of Queensland, South Brisbane, Australia; Children's Health Queensland Hospital and Health Service, Herston, Queensland
Jeffrey Craig, School of Medicine, Deakin University, Geelong, Australia
Melissa Kirkovski, School of Psychology, Deakin University, Geelong, Australia
Natalie T. Mills, Adelaide Medical School, The University of Adelaide, Adelaide, Australia
Nicole J. Rinehart, School of Psychology, Deakin University, Geelong, Australia
Peter H. Donaldson, School of Psychology, Deakin University, Geelong, Australia
Talitha C. Ford, School of Psychology, Deakin University, Geelong, Australia
Karen Caeyenberghs, School of Psychology, Deakin University, Geelong, Australia
Natalia Albein-Urios, School of Psychology, Deakin University, Geelong, Australia
Soukayna Bekkali, School of Psychology, Deakin University, Geelong, Australia
Paul B. Fitzgerald, Central Clinical School, Monash University; Epworth Centre for Innovation in Mental Health, Epworth HealthCare, Camberwell, Australia

Word count (excluding title page, abstract, references, figures and tables): 3,553

*Correspondence to: Peter G. Enticott, School of Psychology, Deakin University, 221 Burwood Hwy, Burwood, Victoria, 3125, Australia.
Email: peter.enticott@deakin.edu.au

v1, 26 October 2020

ABSTRACT

Introduction

There are no well-established biomedical treatments for the core symptoms of autism spectrum disorder (ASD). A small number of studies suggest that repetitive transcranial magnetic stimulation (rTMS), a non-invasive brain stimulation technique, may improve clinical and cognitive outcomes in ASD. We describe here the protocol for a funded multicentre randomised controlled clinical trial to investigate whether a course of rTMS to the right temporoparietal junction (rTPJ), which has demonstrated abnormal brain activation in ASD, can improve social communication in adolescents and young adults with ASD.

Methods and analysis

This study will evaluate the safety and efficacy of a four-week course of intermittent theta burst stimulation (iTBS, a variant of rTMS) in ASD. Participants meeting criteria for DSM-5 ASD (n = 150, aged 14-40 years) will receive 20 sessions of either active iTBS (600 pulses) or sham iTBS (in which a sham coil mimics the sensation of iTBS, but no active stimulation is delivered) to the rTPJ. Participants will undergo a range of clinical, cognitive, epi/genetic, and neurophysiological assessments before and at multiple time points up to six months after iTBS. Safety will be assessed via a structured questionnaire and adverse event reporting. The study will be conducted from November 2020 to October 2024.

Ethics and dissemination

The study was approved by the Human Research Ethics Committee of Monash Health (Melbourne, Australia) under Australia's National Mutual Acceptance scheme. The trial is registered (prospectively) at the Australian New Zealand Clinical Trials Registry (ANZCTR) ACTRN12620000890932p, will be conducted according to Good Clinical Practice, and findings will be written up for scholarly publication.

Strengths and limitations of this study

- This multisite randomised controlled trial will be the largest trial of rTMS in ASD to date
- rTMS will be applied to rTPJ, a cortical region that has demonstrated abnormal activation in ASD and forms a major hub of the "social brain" subnetwork
- Participants will undergo structural MRI scans, with rTMS coil position determined via individualised neuronavigation
- Adolescent and young adult participants will receive rTMS interventions as outpatients, and complete a comprehensive range of clinical, neuropsychological, and neurophysiological assessments
- A limitation of the study is the use of only a sham control condition, rather than an additional "active control" site to determine whether effects are specific to rTPJ (rather than a general effect of brain stimulation)

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that impacts a range of domains, including social communication, behaviour, cognition, emotion regulation, and sensorimotor function[1]. Core symptoms of ASD include social interaction and communication problems, and restricted and repetitive behaviours. Comorbid neurodevelopmental disorders (e.g., attention deficit hyperactivity disorder [ADHD]) and psychiatric disorders (e.g., depression, anxiety) are very common[2 3], with the latter often associated with the core social communicative difficulties[4 5].

Despite the high prevalence of ASD (1 in 59[6]), few clinical interventions target core symptoms beyond early-middle childhood. ASD diagnosis typically occurs by the age of 4-6 years[6], and early, intensive intervention throughout these years is associated with the best outcomes for individuals with ASD and their families[7]. Unfortunately, there is little clinical support available for adolescents and young adults with ASD, who often continue to experience social communication symptoms that result in barriers to education, employment, and community participation. As noted, this group also experiences extremely poor mental health that is much worse than the general population; for instance, lifetime depression and anxiety rates are estimated at 37% and 42%, respectively[2].

Non-invasive brain stimulation (NIBS) has emerged as a novel, safe, and efficacious intervention for a range of brain-based disorders. These techniques allow non-invasive modulation of specific brain regions via electromagnetic or electrical stimulation. The most common of these is repetitive transcranial magnetic stimulation (rTMS), which is now widely used as an intervention for treatment-resistant major depressive disorder[8]. It has also been established as an intervention for other neurological disorders, including migraine and obsessive-compulsive disorder[9 10].

rTMS is administered via a plastic-coated metallic coil that is held against the scalp. This coil emits focal, time-varying electromagnetic pulses, which induce electrical current in superficial cortical tissue, thus stimulating neurons in the local region. Depending on the frequency and strength of pulses administered, rTMS can be used to either enhance cortical excitability (i.e., upregulate neural activity), or decrease cortical excitability (i.e., downregulate neural activity) in the stimulated region. This is particularly useful when targeting regions (or nodes) of brain networks known to be either underactive or overactive in particular conditions. For instance, high-frequency (excitatory) rTMS has been used to stimulate underactive left dorsolateral prefrontal cortex (DLPFC) in treatment-resistant depression[11], while low-frequency (inhibitory) rTMS has been used to downregulate excessive activity in left auditory cortex in schizophrenia[12] and supplementary motor area (SMA) in Tourette's disorder[13]. Importantly, rTMS also influences broader brain networks that involve the stimulated region[14 15], and this is thought to contribute to its clinical efficacy. Here we will stimulate the right temporoparietal junction (rTPJ), a key node for social cognition, which is a typical area of difficulty among individuals with ASD [16].

The brain functions as a set of interconnected networks disseminating neuronal information across a broad range of distributed areas [17]. From a neurobiological perspective, ASD is commonly understood as a disorder of synaptic plasticity and neural connectivity, leading to

abnormalities in brain network connectivity between brain regions. These appear to be mediated by disruptions in both excitatory (e.g., glutamatergic) and inhibitory (e.g., GABAergic) processes[18 19]. There are also well-documented abnormalities in local "node" activity, particularly within networks that comprise the so-called "social brain," including rTPJ[20 21]. Indeed, the rTPJ shows consistent differences in activation between those with and without ASD[16 20-22], while meta-analysis demonstrates reduced rTPJ functional connectivity in ASD [23]. Accordingly, rTMS to this region has the potential to modulate local and regional brain activity within networks implicated in the core social symptoms of ASD.

rTMS is considered a very safe and tolerable technique. It is typically administered by an experienced clinician (nurse or physician), and patients are monitored throughout and at the completion of rTMS administration. Clinical researchers have established a detailed set of safety guidelines, and when rTMS is administered within guideline parameters serious adverse effects are exceedingly rare[24 25]. NIBS (including rTMS) is also considered very safe for paediatric populations, with a recent study showing no adverse effects across 382 children aged 0-18 years[26].

Previously, NIBS has been used to investigate the neuropathophysiology of ASD[27-30]. More recently, several research groups (including ours) have investigated whether rTMS could have clinical utility as an intervention in ASD., These studies (see systematic reviews[31-33]) indicate that: low-frequency stimulation of the DLPFC can reduce repetitive behaviours, improve neurophysiological markers of perception, and reduce irritability; low-frequency SMA stimulation can improve movement-related cortical potentials, and; low-frequency stimulation of the premotor cortex can improve sensorimotor integration. While promising, these studies are hampered by small sample sizes a lack of an appropriate control condition (placebo or sham stimulation), and moderate-to-high risk of bias[31].

At present, only two placebo-controlled randomised controlled trials (RCTs) have been conducted, both of which were double-blind. The first demonstrated that two weeks of daily, high-frequency rTMS to bilateral dorsomedial prefrontal cortex (dmPFC), compared to sham rTMS, improved self-report social relating symptoms in adults with ASD (n = 28) one-month after intervention completion[34]. A recent study demonstrated that four weeks of high-frequency stimulation of bilateral DLPFC did not improve executive function in adolescents and young adults with ASD (n = 40)[35]. There was, however, evidence for a beneficial effect of rTMS for those with lower adaptive functioning at baseline. While providing preliminary, placebo-controlled support for rTMS in ASD, these studies are limited by small sample size.

Rationale/Justification

A recent international "consensus statement" provides recommendations for future rTMS research in ASD[36]. Considering the clinical heterogeneity of ASD, there is agreement that "large, multisite, double-blind, placebo-controlled trials with carefully selected neurobiological targets and outcome measures" are required. It is also necessary to understand variability in the response to rTMS that can lead to an individualised therapeutic approach (i.e., personalised medicine approach). These include demographic (e.g., age, sex), clinical (e.g., disorder severity, cognitive/symptom profile), neurobiological (e.g., cortical

thickness, structural and functional connectivity), and genetic/epigenetic factors. Accordingly, we will conduct a large-scale, multi-site investigation of the safety and efficacy of rTMS in ASD that involves (a) feasible and tolerable stimulation paradigms, (b) a carefully selected neurobiological target and mode of stimulation, and (c) rigorous methodological approaches, including individualised stereotactic neuronavigation, an appropriate control condition, and efficacious double blinding. If successful, this trial will establish a first biomedical intervention to improve social communicative symptoms in adolescents and young adults diagnosed with ASD, and inform on factors associated with intervention response, with anticipated benefits in mental health, quality of life, and social participation.

Research Hypotheses

In ASD, active rTMS to rTPJ, when compared to sham rTMS, will be associated with:

1. Improved social communication, measured using the Social Responsiveness Scale – 2nd Edition (SRS-2) (evident one-month after end of rTMS, maintained at three- and six-months) (primary outcome);
2. Improved social cognitive performance, measured using face processing/face emotion processing neuropsychological tasks (evident immediately after rTMS, maintained at one-, three-, and six-months);
3. Improved quality of life, measured using the Personal Wellbeing Index (evident one-month after rTMS, maintained at three- and six-months);
4. Acceptable tolerability and safety (as measured by a structured interview and adverse event reporting).

METHODS AND ANALYSIS

Study Design and Participants

This is a four-year multicentre Australian study to assess the safety and efficacy of a four-week course of rTMS to improve social communication in adolescents and young adults diagnosed with ASD. It will be a parallel group (between-subjects), double-blind, placebo-controlled RCT. Participants will be 150 individuals meeting criteria for DSM-5[1] ASD and aged between 14-40 years. They will be recruited through existing research participant databases, the Australian Autism Biobank[37], and advertisements in local clinics, advocacy/support groups, and via social media. The research team will also engage popular media, both locally and nationally, to promote recruitment.

The study will be overseen by a Research Management Group, which comprises the ten Chief Investigators, Study Coordinator, and Site Coordinators. They will meet monthly via videoconference for the duration of the trial. There will be 30 participants enrolled at each of the cities involved (Brisbane, Sydney, Melbourne, Adelaide, Perth). Participants will undergo 20 intervention sessions (one per weekday for four consecutive weeks) of either active or sham (i.e., placebo) rTMS. Participants will be assessed before and up to 6 months after intervention and in accordance with Good Clinical Practice (GCP). Assessments will evaluate social communication, neuropsychological function, quality of life, safety, and tolerability. There will be five primary intervention sites within Australia (Brisbane, Sydney,

Melbourne, Adelaide, Perth) and additional local sites to support recruitment, assessment, genetic analysis, and neuroimaging. These will include both University and hospital sites. Written informed consent will be obtained from participants (or their parent/guardian in the case of minors, aged 14-17 years) by a local Chief Investigator or Site Coordinator. Model participant Information and consent forms for parents/guardians and adult participants are provided as Supplemental Material.

Patient and Public Involvement

The research team have engaged in extensive consultation with community groups in recent years, including multiple community forums on rTMS). We have also consulted with autism organisations when preparing advertisements and other study-related communications. While participants were not directly involved in the design of this specific trial, throughout the study we will engage a range of community and advocacy groups in the implementation of the research, and health service partners to ensure rapid translation of our research findings to clinical practice. For instance, the Telethon Kids Institute (Western Australia) have established a community reference group with whom they regularly consult for consumer involvement, and this group will also be engaged for the current trial.

rTMS Protocol

Participants will receive standard intermittent theta burst stimulation (iTBS) to the rTPJ each consecutive weekday for a four-week period (20 sessions). They will undergo either active iTBS or sham iTBS, where a "sham coil" is used to mimic the appearance, sound, and sensation of rTMS, but without delivering electromagnetic stimulation.

Participants will undergo 3T T1 magnetic resonance imaging (MRI) prior to the first rTMS session, and stereotactic neuronavigation will be used to determine the site of stimulation (MNI coordinates x = 56, y = -56, z = 18; see Figure 1).

All stimulation will be administered via a Magstim Rapid^2 stimulator (The Magstim Company Ltd., Wales, UK). A staff member trained in rTMS will deliver all rTMS interventions. A visual resting motor threshold (i.e., visual observation of muscle activation following TMS pulse) will be determined at the right hemisphere/left hand prior to the first rTMS session. Each iTBS is delivered with the following stimulation parameters:

- Burst pattern: 3 pulses delivered at 50 Hz
- Train duration: Bursts repeated 5 times per second (5 Hz) for 2 seconds (10 bursts)
- Intensity: 70% of resting motor threshold
- Inter-train interval: 8 seconds
- Total time: 200 seconds (3 minutes, 20 seconds)
- Total trains: 20
- Total bursts: 200
- Total pulses: 600

<<Insert Figure 1 around here>>

Figure 1. Site of rTMS coil localisation (MNI coordinates x = 56, y = -56, z = 18)

Participants will be monitored by study staff for at least five minutes after each intervention session. They can then leave the facility and go about their normal daily activities, including driving. The participant will be administered the Non-invasive Brain Stimulation Post-Stimulation Interview at the end of each week of rTMS intervention (i.e., after the Friday session) to determine the presence/intensity of any side-effects. For child participants (aged 14-17 years), this interview will be conducted with both the parent/guardian and the child.

Inclusion and Exclusion Criteria

Inclusion Criteria

- Aged 14-40 years
- Meets criteria for ASD based on DSM-5 criteria (clinician reported), and confirmed via Autism Diagnostic Observation Schedule – Second Edition (ADOS-2)
- English-language fluency/proficiency

Exclusion Criteria

- History of seizure/s or epilepsy
- History of severe (traumatic) brain injury
- Contraindication to MRI (e.g., claustrophobia, metal implants)
- Formal verbal intelligence quotient VIQ assessment <55, as determined by Wechsler Abbreviated Scale of Intelligence (WASI-2)
- Comorbid neurological or psychiatric diagnosis not commonly associated with ASD (e.g., psychosis)
- Unstable medical condition
- Unstable medication regimen, or medication contraindicated for TMS
- Pregnancy or current breastfeeding
- Substance use/abuse disorder
- Concurrent intervention targeting social communication
- Evidence of significant epileptiform activity on electroencephalogram (EEG) (e.g., seizures on EEG, runs of epileptiform discharges)

Outcome Measures

Data collection and study timings are presented in Table 1. Participants are assessed prior to rTMS (T0), and at four points after rTMS: T1 (immediately after rTMS), T2 (one-month after completion of rTMS), T3 (three-months after completion of rTMS), and T4 (six-months after completion of rTMS).

The primary outcome measure is the Social Responsiveness Scale – 2nd Edition (SRS-2; School-Age AutoScore Form for Parent/Guardian [parent/guardian report]/Adult AutoScore Form for Informant [informant report]) Total T-score, while the primary outcome point will be at 1-month after completion of rTMS (T1) compared with pre-rTMS (T0). For adult participants, an informant (parent/relative/friend) will complete the SRS-2 with respect to the participant.

Secondary outcomes encompass a range of clinical, neuropsychological, neurophysiological, and biological measures. Clinical measures include: Conners 3 (parent/guardian report)/Conners Adult ADHD Rating Scales (CAARS) (informant report and adult self-report); Aberrant Behaviour Checklist – Second Edition (ABC-2) (parent/guardian/informant report); Behaviour Rating Scale of Executive Function, Second Edition (BRIEF)/ Behaviour Rating Scale of Executive Function – Adult Version (BRIEF-A) (parent/guardian/informant report and adult self-report); World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) (parent/guardian/informant report); Depression, Anxiety and Stress Scale (DASS) (self-report); and Personal Wellbeing Index (PWI) (self-report).

Neuropsychological measures include: Reading the Mind in the Eyes Test (RMET); Benton Facial Recognition Test (BFRT); Cambridge Face Memory Test (CFMT); NIH Cognition Toolbox; and Working Memory Assessment.

Neurophysiological measures include: resting-state electroencephalography (EEG); and face processing event-related potentials (ERP).

Finally, a buccal swab will be administered both before and after the course of rTMS, which will allow an investigation of genetic and epigenetic predictors of intervention response, and potential epigenetic changes following rTMS.

<<Insert Table 1 around here>>

Randomisation

There will be an equal number of participants allocated to each condition at each of the five project sites (15 active, 15 sham; total 75 active, 75 sham). A computerised adaptive randomisation procedure (minimisation method) will be performed, adjusting for baseline characteristics (age, sex, SRS T0 score)[38], which ensures a balance of conditions across trial sites. Randomisation will be completed by the Study Coordinator, who will provide this information to the intervention clinicians (who are not blinded) via email.

Statistical Analysis and Data Management

Upon enrolment, participants will be allocated a unique study identification code. Their name will not appear with the research data collected. All data will be stored in REDCap[39] and on secure network locations governed by Deakin University. All Chief Investigators will have access to the final trial dataset. Any information obtained in connection with this research project that can identify a participant will remain confidential. Where a participant elects to withdraw from the study, we will retain and use any data collected prior to withdrawal.

Random effects linear mixed models will be used to ensure the inclusion of participants who have missing data, including those that withdraw from the study. Specifically, this will involve a between-subjects factor (rTMS condition: active vs. placebo) and a within-subjects factor (time of assessment: pre vs. post vs. one-month vs. three-months vs. six-months), with participant and site entered as random effects. We will examine rTMS safety by

exploring descriptive statistics arising from the structured questionnaire related to the development of possible side-effects. An interim analysis will be performed at the mid-point of data collection for possible trial futility.

Exploratory analyses will be undertaken to investigate factors, including genetic variants and structural/functional neuroimaging (e.g., diffusion MRI, resting-state functional MRI), that influence intervention response, and to investigate epigenetic changes following rTMS. We will use linear mixed models to determine the effect of rTMS on SRS-2 score, but with additional independent variables (e.g., age, sex, cognitive ability, ADOS-2 symptom severity, rTPJ structural and functional connectivity within the social brain subnetwork, polygenic risk score [PRS] for ASD[40]).

Epigenetic variation refers to variation in chromatin structure, which is associated with variation in gene expression. In contrast to DNA, epigenetic variation can change over time, for example following treatment[41]. Accordingly, we will compare epigenetic variation for DNA samples collected before and after rTMS and investigate any associations with intervention response. (See Supplemental Material for a statement on Biological Specimens.)

At the conclusion of the project, all electronic and hard copy data will be archived within Deakin University (Information and Records Services). Electronic data will be retained on secure Deakin University servers and archived in REDCap, but also transferred to physical hard drives for archival storage. As some hard copy data will be stored at each site (e.g., signed consent forms, clinical files used during rTMS intervention), these will be securely couriered to Deakin University for archiving. Each site will be required to delete any electronic data that may remain at their site. As this is a clinical trial involving child participants, data will be retained indefinitely. Any published work from this study will be accompanied by publicly available deidentified data through the Open Science Framework (osf.io). The research team, including both Chief Investigators and Associate Investigators, all have the opportunity to conduct secondary analyses. This will be negotiated with the trial's Research Management Group, which comprises the ten Chief Investigators. Data may also be shared with external (national and international) collaborators to obtain larger sample sizes, which are often necessary to achieve the statistical power necessary to analyse biomarker data. This could include specific research projects or online data repositories, which may be accessed and used by external researchers.

Blinding

This is a double-blind study; accordingly, participants (and their parents/guardians, where relevant) and the testing researchers/statisticians will be blinded to intervention condition. The individual administering rTMS must select the appropriate coil (i.e., active or sham) and will therefore not be blinded, but this individual will not conduct any of the assessment or be involved in the statistical analyses. Unblinding may occur in the event of an adverse event. At the conclusion of the final assessment (T4), participants will be unblinded as to their intervention condition by a member of the research team who is not blinded. Those who were allocated to the sham rTMS intervention will be offered the opportunity to undergo the real rTMS intervention.

Table 1.

Data Collection and Study Timings

Visits	Pre-enrolment	T0	Tx	T1	T2	T3	T4
Screening	X	X					
Written informed consent		X					
Randomisation		X					
Demographics	X	X					
Medical History	X	X					
Neuroimaging (MRI)		X					
Clinical EEG		X					
Buccal Swab		X		X			
ADOS-2		X					
WASI-2		X					
rTMS intervention (active/sham)			X				
NIBS:PSI			X				
SRS-2		X		X	X	X	X

Conners-3/CAARS	X	X	X	X	X
ABC-2	X	X	X	X	X
BRIEF/BRIEF-A	X	X	X	X	X
DASS	X	X	X	X	X
PWI	X	X	X	X	X
WHODAS 2.0	X	X	X	X	X
NIH Cognition Toolbox	X	X	X		X
RMET	X	X	X		X
BFRT	X	X	X		X
CFMT	X	X	X		X
Working Memory	X	X	X		X
rsEEG	X	X			
FP-ERP	X	X			

Notes: T0: Pre-rTMS; T1: week following rTMS; T2: one-month after completion of rTMS; T3: three-months after completion of rTMS; T4: six-months after completion of rTMS; MRI: magnetic resonance imaging; ADOS-2: Autism Diagnostic Observation Schedule, 2nd Edition; WASI-2: Wechsler Abbreviated Scale of Intelligence, 2nd Edition; rTMS: repetitive transcranial magnetic stimulation; NIBS:PSI: Non-invasive Brain Stimulation Post-stimulation Interview; SRS-2: Social Responsiveness Scale, 2nd Edition; CAARS: Conners Adult ADHD Rating Scales; ABC-2: Aberrant Behaviour Checklist, 2nd Edition; BRIEF: Brief Rating Inventory of Executive Function; BRIEF-A: Brief Rating Inventory of Executive Function – Adult Version; DASS: Depression Anxiety Stress Scale; PWI: Personal Wellbeing Index; WHODAS 2.0: World Health Organisation Disability Assessment Schedule; NIH: National Institutes of Health; RMET: Reading the Mind in the Eyes Test; BFRT: Benton Facial Recognition Test; CFMT: Cambridge Face Memory Test; rsEEG: resting-state electroencephalography; FP-ERP: face-processing event-related potentials.

Safety

Participants will undergo extensive screening to ensure that they meet safety criteria for undergoing rTMS[25]. For child participants, a parent or legal guardian will complete the screening. Participants will undergo EEG prior to their first rTMS session, and this will be reviewed by the trial neurologist. Any participants demonstrating evidence of runs of epileptiform discharges, as assessed by the study neurologist, will be withdrawn from the study. At the beginning of their first session, participants (or their parent/guardian for child participants) will again be screened to ensure that they can undergo rTMS.

A data safety monitoring board (DSMB) will be formed. This DSMB will comprise three senior clinical researchers independent to the current project. The DSMB will meet twice per year to review the conduct of the trial and monitor study data. They will also review any serious adverse events in a mid-trial safety analysis and on an *ad hoc* basis. Terms of reference will be based on advice from the National Health and Medical Research Council's Data Safety Monitoring Boards documentation.

Adverse events will be reported to the relevant Human Research Ethics Committees (HREC) immediately, and no later than 72 hours after the event. Depending on the nature and severity of the event, it may be necessary to also report to other regulatory bodies (e.g., Therapeutic Goods Administration) and suspend or terminate the trial. Should an individual suffer harm from trial participation, they will receive medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

ETHICS AND DISSEMINATION

This study has been approved by the Monash Health Human Research Ethics Committee (Melbourne, Australia; RES-20-0000-606A) under the National Mutual Acceptance scheme, which allows for mutual scientific and ethic acceptance across Australian jurisdictions and institutions. We will engage a range of community and advocacy groups in the implementation of the study, and health service partners to ensure rapid translation of our research findings to clinical practice.

The health outcomes of this study will be provided within 12 months of the trial's completion, initially through a freely accessible preprint and an open-access peer-reviewed journal publication. Authorship will be determined according to the standards outlined in the National Health and Medical Research Council's *Australian Code for the Responsible Conduct of Research*. Chief Investigators will also present the study findings at relevant scientific conferences and autism advocacy/support group community forums. The research team will also engage in more extensive public outreach and disseminate study findings widely through appropriate channels (e.g., study website, social media, news outlets). These dissemination pathways will also involve contributing to clinical guidelines (and direct engagement with healthcare providers).

Participants will be sent a plain language summary detailing the study results at the completion of the trial. This summary will be written as a lay summary and in a manner

accessible to participants and their families. A child version will also be sent to parents/guardians to share with their child. The summary will contain no identifying information and provide only group level results.

This project involves the collection of a large number of measures (e.g., clinical, neuropsychological, neuroimaging, genetic/epigenetic) and it is expected that the Chief Investigators will conduct further exploratory analyses on these data. This might include, for example, examining neuroimaging and genetic predictors of response to rTMS intervention and characterising epigenetic changes following rTMS.

TRIAL STATUS

At the time of submission recruitment has not commenced.

AUTHORS' CONTRIBUTIONS

PE, KB, IH, ML, NR, CM, SC, AV, KB, AG, HH, JC, MK, PD, and PF contributed to the design of the study.
PGE, KB, ML, NR, CM, SC, AV, KB, AW, GA, MK, PD, TF, KC, NA, SB, and PF contributed to the writing of the manuscript.
All authors approved the final draft of the manuscript.

FUNDING

This project has been funded by the National Health and Medical Research Council (NHMRC) under the Medical Research Future Fund (MRFF) Neurological Disorders 2020 scheme (Application ID: APP1199298).

PROJECT REGISTRATION

This project has been prospectively registered on the Australian New Zealand Clinical Trials Registry (ANZCTR; ACTRN12620000890932p).

COMPETING INTERESTS

There are no competing interests to declare.

TRIAL SPONSOR

Deakin University

Contact: Prof. Peter G. Enticott
221 Burwood Hwy, Burwood
Victoria, 3125, AUSTRALIA

ROLE OF SPONSOR AND STUDY

This is an investigator-initiated study funded by the Australian Government, who provided peer review but have had no other involvement in the trial.

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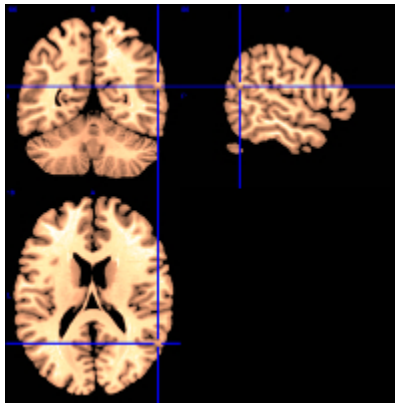

Figure 1

Insert Header with institution's name or institution's letterhead

Participant Information Sheet/Consent Form

Interventional Study - *Adult providing own consent*

[Insert site name]

Title	*Does repetitive transcranial magnetic stimulation (rTMS), compared to sham rTMS, improve social communication in adolescents and young adults with autism spectrum disorder (ASD)?*
Short Title	*MRFF TBS-ASD*
Protocol Number	*v2, 11/09/2020*
Project Sponsor	*Deakin University*
Coordinating Principal Investigator	*Prof. Peter Enticott*
Associate Investigator(s)	*Prof. Paul Fitzgerald, A/Prof. Karen Barlow, Prof. Ian Hickie, Dr Melissa Licari, Dr Nigel Rogasch, Prof. Christel Middeldorp, Dr Scott Clark, Dr Ann-Maree Vallence, Dr Kelsie Boulton, Prof. Adam Guastella, Prof. Andrew Whitehouse, Prof. Cherrie Galletly, Dr Gail Alvares, Dr Hakuei Fujiyama, A/Prof. Helen Heussler, A/Prof. Jeffrey Craig, Dr Melissa Kirkovski, Dr Natalie Mills, Prof. Nicole Rinehart, Dr Peter Donaldson, Dr Talitha Ford, Prof. Karen Caeyenberghs*
Location	*[Insert site-specific location]*

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 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 and 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 rTMS can be used to improve social function. rTMS is a safe and non-invasive means of stimulating nerve cells in a particular part of the brain via the administration of brief magnetic pulses. rTMS has been developed as a treatment for major depressive disorder, and we have previously found that rTMS can benefit social aspects of ASD.

In this study we will stimulate a region of the brain that is involved in social understanding and social communication. This region is called the right temporoparietal junction, or rTPJ.

Some participants will receive the real form of rTMS, while others will receive a sham or placebo form. The sham or placebo form mimics the feeling of rTMS, but no brain stimulation is delivered. You will not know which one you receive until the end of your involvement in the study. Those who received the sham or placebo form will be given the opportunity to undergo the real rTMS treatment at the end of their involvement in the study.

150 people (aged 14-40 years) will take part in this study, which is being conducted throughout Australia. There are sites in Brisbane, Sydney, Melbourne, Adelaide, and Perth. Participants will be recruited from around Australia, but primarily the greater metropolitan regions within these five cities.

rTMS 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, Prof. Peter Enticott (Deakin University, Melbourne). This research has been funded by the National Health and Medical Research Council (NHMRC) of Australian through a Medical Research Future Fund grant (MRFF RCRDUN Neurological Disorders 2020; Application APP1199298).

3 What does participation in this research involve?

You will be participating in a randomised controlled research project. Sometimes we do not know which treatment is best for treating a condition. To find out we need to compare different treatments. We put people into groups and give each group a different treatment (in this case, real rTMS vs. sham/placebo rTMS). The results are compared to see if one is better. To try to make sure the groups are the same, each participant is put into a group by chance (random).

This is a double-blind study. This means that neither you nor your study doctor will know which treatment you are receiving (in this case, real rTMS or sham/placebo rTMS). However, in certain circumstances your study doctor can find out which treatment you are receiving. Participants will be randomly allocated to either the real rTMS or sham/placebo rTMS condition. As mentioned, those allocated to the sham or placebo form will be given the opportunity to undergo the real rTMS treatment at the end of their involvement in the study.

This research project has been designed to make sure the researchers interpret the results in a fair and appropriate way and avoids study doctors or participants jumping to conclusions.

If you decide to take part in this project, you will be asked to take part in a number of interviews and procedures over the course of approximately eight months. These are outlined below.

Prior to completing the study, we will need to determine your eligibility to take part in the study. We will do this by asking you questions (either over the phone or via email) about your health. 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.

Assessment Session One: The first assessment will take place at [site-specific location]. It will take approximately three hours, but you will be given regular breaks throughout the session.

We will begin by asking you some questions about your health, which will help to confirm your eligibility to take part in the study. 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 (e.g., a parent, sibling, spouse, or close friend) complete a series of questionnaires. You can nominate this person and we will ask that they agree to complete these questionnaires now and another four times during the study.

You will then complete a short cognitive assessment, which involves solving puzzles and describing what different words mean.

Finally, you will undergo electroencephalography (EEG), which involves wearing an "electrode cap" to measure the electrical activity of your brain, or your "brainwaves." The electrode cap feels similar to a swimming cap. It will also feel a little damp, as we need to put a small amount of gel or saline into the cap to ensure that we get accurate recordings. For most of the EEG you will simply rest while sitting in a chair, but you will also complete a short task on a computer that involves looking at different objects (e.g., faces, household furniture, butterflies).

Assessment Session Two: Around one-week after "Assessment Session One" you will then undergo a magnetic resonance imaging (MRI) brain scan at [site-specific location]. The MRI brain scan takes around 45-60 minutes, during which you will be asked to lie still in an MRI scanner. (Please note that with preparation time you attend the MRI facility for up to two hours.) MRI is a routinely performed, painless ways of examining brain structure and activity. We will use the MRI to accurately place the rTMS device, and ensure that we are stimulating the correct brain region. The MRI procedure may also help us better understand how the treatment works and to determine who is likely to respond to treatment and why.

Assessment Session Three: During the same week of "Assessment Session Two," you will attend a two-hour assessment session at [site-specific location]. Here we will ask you questions about yourself, some of which are relevant to ASD, while others relate to your mood, concentration, stress, and your satisfaction with life. We will also ask you to complete some cognitive tasks on a computer/tablet. These tasks measure your memory, attention, and understanding of other people's emotions. We will also ask you to provide a sample for genetic analysis; this will involve having a cotton swab rubbed against the inside of your cheek. These genetic analyses are conducted to investigate whether people with certain genetic profiles respond better to the intervention. You will not receive any health information from these genetic analyses, and they are not considered to be clinically informative.

rTMS Intervention (4 weeks): The week after "Assessment Session Three" you will begin the rTMS intervention, which involves attending [site-specific location] and receiving rTMS for 3 minutes, 20 seconds each consecutive weekday for a four-week period (20 rTMS sessions in total).

You will have your first rTMS session on the Monday after "Assessment Session Three." At the beginning of the first session 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 rTMS treatments. 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.

During each rTMS session you will be awake, alert, and aware of what is happening at all times. During rTMS a coil will be placed against the head, through which rTMS 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 sensations associated with rTMS are mild, and most people describe it as a "tapping" sensation on their head. During a rTMS procedure you will hear clicking sounds as the current passes through the coil. You will wear earplugs so that this noise doesn't disturb you.

Including setup time, each subsequent treatment session should only take approximately 10 minutes. At the end of each treatment week (i.e., on the Friday session) we will ask you a number of questions about your experience of RTMS, and whether you feel you have experienced any side effects.

Assessment Session Four: The week after your last rTMS session, you will attend another two-hour assessment session at [site-specific location]. Here we will again ask you questions about yourself, some of which are relevant to ASD, while others relate to your mood, concentration, stress, and satisfaction with life. We will also again ask you to complete some cognitive tasks on a computer/tablet and to provide another sample (cheek swab) for genetic analysis.

Assessment Session Five: One-month after your last rTMS session, you will attend another two-hour assessment session at [site-specific location]. This session will be identical to Assessment Session Four.

Assessment Session Six: Three-months after your last rTMS session, you will attend a one-hour assessment session at [site-specific location]. This session will be identical to Assessment Session Five except that you will not complete the computerised cognitive tasks.

Assessment Session Seven: Six-months after your last rTMS session, you will attend a final two-hour assessment session at [site-specific location]. This session will be identical to Assessment Session Five. Following the assessment, you will be unblinded; that is, a member of the research team will tell you which treatment condition you received (i.e., real or sham/placebo). If you received the real treatment, your involvement in the study will conclude. If you received the sham/placebo condition, you will be given the opportunity to receive the real treatment and can liaise with research staff to determine when you would like to undergo this four-week treatment.

There are no costs associated with participating in this research project. All treatments, tests, and medical care required as part of the research project will be provided to you free of charge.

You will not be paid for your participation in this research, but you will be reimbursed $200 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 decide 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.

It is desirable that your local doctor be advised of your decision to participate in this research project. If you have a local doctor, we strongly recommend that you inform them of your participation in this research project.

The research will be monitored by an independent Data Safety Monitoring Board, who will meet twice per year and review the conduct of the trial, monitor study data, and review any serious adverse events that might arise throughout the trial.

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, or evidence of significant seizure activity as assessed by EEG
- 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)
- Being deemed unsuitable to undergo MRI (e.g., due to presence of metal in the body)
- Unstable medical condition
- Unstable medication regime
- Certain medications
- Substance use disorder
- Undergoing another current treatment for social communication
- Employment as a professional driver or machine operator (as the event of a seizure may affect employment)
- Pregnancy (female participants for whom child-bearing is a possibility will be required to undergo a urine screen)
- Certain neurological or psychiatric diagnoses (i.e., those not commonly associated with ASD, such as psychosis)
- A measured verbal intelligence quotient (IQ) of less than 55

5 Other relevant information about the research project

This study is only taking place in Australia. There will be 150 participants in this study, with 30 taking part in each of the five cities involved: Brisbane, Sydney, Melbourne, Adelaide, and Perth. There are a total of 14 organisations involved, including Universities, hospitals, and medical centres. This study is a follow-on study from our previous trials of rTMS in ASD, which have taken place at Monash University, Deakin University, The Alfred hospital, and the Epworth Camberwell.

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 *[site-specific Institution/s]*.

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 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?

Repetitive Transcranial Magnetic Stimulation (rTMS)

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.

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 rTMS and is thought to affect approximately 3% or 3 in 100 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, ibuprofen, 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 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 such individuals). If you have ever experienced a seizure, or if your EEG shows evidence of epileptiform activity, 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 rTMS 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 rTMS. Staff will monitor you and know how to treat a seizure should one occur.

The effects of rTMS 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 urinal pregnancy test prior to commencing rTMS. This test will be processed by a female member of the research staff.

If you do become pregnant whilst participating in the research project, you should advise research staff immediately. The researchers 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 rTMS.

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

Magnetic Resonance Imaging (MRI)

MRI stands for magnetic resonance imaging. An MRI scanner is a machine that uses electromagnetic radiation (radio waves) in a strong magnetic field to take clear pictures of the inside of the body. Electromagnetic radiation is not the same as ionising radiation used, for example, in X-rays. The pictures taken by the machine are called MRI scans.

There are no proven long-term risks related to MRI scans as used in this research project. MRI is considered to be safe when performed at a centre with appropriate procedures. However, the magnetic attraction for some metal objects can pose a safety risk, so it is important that metal objects are not taken into the scanner room.

We will thoroughly examine you to make sure there is no reason for you not to have the scan. You must tell us if you have metal implanted in your body, such as a pacemaker or metal pins.

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 become uncomfortable during the session, we can pause or stop the scanning.

The scans we are taking are for research purposes. They are not intended to be used like scans taken for a full clinical examination. The scans will not be used to help diagnose, treat, or manage a particular condition. A specialist will look at your MRI scans for features relevant to the research project. On rare occasions, the specialist may find an unusual feature that could have a significant risk to your health. If this happens, we will contact you to talk about the findings. We cannot guarantee that we will find any/all unusual features. 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.

If you become upset or distressed as a result of your participation in the research, the study doctor will be able to arrange for counselling or other appropriate support. Any counselling or support will be provided by qualified staff who are not members of the research project team. This counselling will be provided free of charge.

9 What will happen to my test samples?

You will be asked to provide additional consent for the collection of your tissue (i.e., cheek swab) during the research project. As noted, these samples are collected to allow us to investigate whether certain genetic profiles are associated with a better response to the rTMS intervention. We will only conduct these analyses at a group level. You will not receive any health information (e.g., genetic disease predisposition) from these genetic analyses, and they are not considered to be clinically informative. Your genetic material and information, where

identified or potentially identifiable, will not be released for other uses without your prior consent, unless required by law.

Samples of your tissue obtained for the purpose of this research project will be transferred to the Institute for Molecular Bioscience, University of Queensland, who will charge a fee to the research team to recover some of the costs of storing and administering the tissue samples. The University of Queensland will not transfer or sell your samples to any third party.

10 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, your study doctor might consider it to be in your best interests to withdraw you from the research project. If this happens, your study doctor will explain the reasons and arrange for your regular health care to continue.

11 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 research 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.

Because this trial is assessing the effect of rTMS on social communication, you cannot participate if you are also undergoing any other treatment or intervention for social communication. This includes interventions delivered by psychologists.

12 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 doctor and relevant 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 up to the time you withdraw will form part of the research project results. If you do not want the researchers to do this, you must tell them before you join the research project.

13 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 drug/treatment/device being shown not to be effective
- The drug/treatment/device being shown to work and not need further testing
- Decisions made by local regulatory/health authorities.

14 What happens when the research project ends?

You will be sent a summary of the main findings when the project has been completed. This is a 4-year study and it is expected that study results will be available by late 2024. Your data will then be securely archived at Deakin University.

Please note that rTMS will not be available from the research sites after completing the study. It may be approved for future use in ASD, but this will depend on the results from the current study.

Part 2 How is the research project being conducted?

15 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. Upon enrolment in the trial you will be allocated a unique study identification code. Your name will not appear with the research data that we collect from you and it will only be possible to re-identify your data using the study code. Only the research team will know which code identifies which participant. Your information will only be used for the purpose of this research project and future research projects, and it will only be disclosed with your permission, except as required by law.

Information about you may be obtained from your health records held at this and other health services for the purpose of this research. By signing the consent form, you agree to the study team accessing health records if they are relevant to your participation in this research project.

Your health records and any information obtained during the research project are subject to inspection (for the purpose of verifying the procedures and the data) by the relevant authorities and authorised representatives of the Sponsor, Deakin University, the institution relevant to this Participant Information Sheet, *[Name of institution]*, or as required by law. By signing the Consent Form, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

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. We will only present group-level findings (e.g., average scores across the group) and no individual data will be reported.

In accordance with relevant Australian *and/or [Name of state/territory]* 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 and for future research 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.

It is expected that deidentified data from this study will be made available to other researchers via online data repositories. You will not be able to be identified in these repositories. It is also possible that the research team will use your data from this research project for future studies, but again you will not be able to be identified.

16 Complaints and compensation

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.

If you have complaints about your treatment by members of staff working on this research project, you should contact the person nominated in Section 19 below. If you have complaints about any of the ethical aspects of this study, you can contact the local reviewing HREC Executive Officer nominated in Section 19 below. Complaints about clinical trials can also be directed to the Office of the Australian Information Commissioner.

17 Who is organising and funding the research?

This research project is being conducted by a team of researchers led by Prof. Peter Enticott from Deakin University, Victoria. It is funded through a Medical Research Future Fund grant from the National Health and Medical Research Council to Prof. Enticott and the research team.

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

18 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 HREC of Monash Health and *[Name of institutions]*.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2018)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

19 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 that may be related to your involvement in the project (for example, any side effects), you can contact your site's principal study doctor on *[phone number]* or any of the following people:

Study contact person

Name	*[Name]*
Position	*[Position]*
Telephone	*[Phone number]*
Email	*[Email address]*

Clinical contact person

Name	*[Name]*
Position	*[Position]*
Telephone	*[Phone number]*
Email	*[Email address]*

For matters relating to research at the site at which you are participating, the details of the local site complaints person are:

Complaints contact person

Name	*[Name]*
Position	*[Position]*
Telephone	*[Phone number]*
Email	*[Email address]*

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 approving this research and HREC Executive Officer details

Reviewing HREC name	*Monash Health*
HREC Executive Officer	*Ms Deborah Dell*
Telephone	*(03) 9594 4605*
Email	*research@monashhealth.org*

Local HREC Office contact (Single Site - Research Governance Officer)

Name	*[Name]*
Position	*[Position]*
Telephone	*[Phone number]*
Email	*[Email address]*

Consent Form - *Adult providing own consent*

Title	*Does repetitive transcranial magnetic stimulation (rTMS), compared to sham rTMS, improve social communication in adolescents and young adults with autism spectrum disorder (ASD)?*
Short Title	*MRFF RTMS-ASD*
Protocol Number	*v2, 11/09/2020*
Project Sponsor	*Deakin University*
Coordinating Principal Investigator	*Prof. Peter Enticott*
Associate Investigator(s)	*Prof. Paul Fitzgerald, A/Prof. Karen Barlow, Prof. Ian Hickie, Dr Melissa Licari, Dr Nigel Rogasch, Prof. Christel Middeldorp, Dr Scott Clark, Dr Ann-Maree Vallence, Dr Kelsie Boulton, Prof. Adam Guastella, Prof. Andrew Whitehouse, Prof. Cherrie Galletly, Dr Gail Alvares, Dr Hakuei Fujiyama, A/Prof. Helen Heussler, A/Prof. Jeffrey Craig, Dr Melissa Kirkovski, Dr Natalie Mills, Prof. Nicole Rinehart, Dr Peter Donaldson, Dr Talitha Ford, Prof. Karen Caeyenberghs*
Location	*[Location where the research will be conducted]*

Consent Agreement

I have read the Participant Information Sheet.

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 *[Name of Institution]* concerning my condition 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 agree for my anonymous study data to be shared with other researchers, including those outside *[Name of Institution]* and outside Australia, for future studies.

I agree to my anonymised data being made available through online repositories and to the use of my data in any future research.

Declaration by Participant – for participants who have read the information

Name of Participant (please print) _____

Signature _____ Date _____

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.

I consent to the storage and use of tissue samples (cheek swabs) taken from me for use, as described in the relevant section of the Participant Information Sheet, for:

- This specific research project
- Other research that is closely related to this research project
- Any future research.

By signing this consent section, I agree to the use of my tissue samples for genetic testing, as outlined in the relevant Section of the Participant Information Sheet.

Name of Participant (please print) _____

Signature _____ Date _____

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	*Does repetitive transcranial magnetic stimulation (rTMS), compared to sham rTMS, improve social communication in adolescents and young adults with autism spectrum disorder (ASD)?*
Short Title	*MRFF RTMS-ASD*
Protocol Number	*v2, 11/09/2020*
Project Sponsor	*Deakin University*
Coordinating Principal Investigator	*Prof. Peter Enticott*
Associate Investigator(s)	*Prof. Paul Fitzgerald, A/Prof. Karen Barlow, Prof. Ian Hickie, Dr Melissa Licari, Dr Nigel Rogasch, Prof. Christel Middeldorp, Dr Scott Clark, Dr Ann-Maree Vallence, Dr Kelsie Boulton, Prof. Adam Guastella, Prof. Andrew Whitehouse, Prof. Cherrie Galletly, Dr Gail Alvares, Dr Hakuei Fujiyama, A/Prof. Helen Heussler, A/Prof. Jeffrey Craig, Dr Melissa Kirkovski, Dr Natalie Mills, Prof. Nicole Rinehart, Dr Peter Donaldson, Dr Talitha Ford, Prof. Karen Caeyenberghs*
Location	*[Location where the research will be conducted]*

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 *[Institution]*.

Name of Participant (please print) _____

Signature _____ Date _____

Description of circumstances where communicated verbally:

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.

Insert Header with institution's name or institution's letterhead

Participant Information Sheet/Consent Form

Interventional Study - *Parent/Guardian consenting on behalf of participant*

[Insert site name]

Title	*Does repetitive transcranial magnetic stimulation (rTMS), compared to sham rTMS, improve social communication in adolescents and young adults with autism spectrum disorder (ASD)?*
Short Title	*MRFF TBS-ASD*
Protocol Number	*v2, 11/09/2020*
Project Sponsor	*Deakin University*
Coordinating Principal Investigator	*Prof. Peter Enticott*
Associate Investigator(s)	*Prof. Paul Fitzgerald, A/Prof. Karen Barlow, Prof. Ian Hickie, Dr Melissa Licari, Dr Nigel Rogasch, Prof. Christel Middeldorp, Dr Scott Clark, Dr Ann-Maree Vallence, Dr Kelsie Boulton, Prof. Adam Guastella, Prof. Andrew Whitehouse, Prof. Cherrie Galletly, Dr Gail Alvares, Dr Hakuei Fujiyama, A/Prof. Helen Heussler, A/Prof. Jeffrey Craig, Dr Melissa Kirkovski, Dr Natalie Mills, Prof. Nicole Rinehart, Dr Peter Donaldson, Dr Talitha Ford, Prof. Karen Caeyenberghs*
Location	*[Insert site-specific location]*

Part 1 What does the child's participation involve?

1 Introduction

This is an invitation for the child in your care to take part in this research project because they have been diagnosed with autism spectrum disorder (ASD). The research project is testing a new treatment for ASD. The new treatment is called 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 your child 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 your child can take part, you might want to talk about it with a relative, friend or your child's local doctor.

Participation in this research is voluntary. If you do not wish your child to take part, they do not have to. Your child will receive the best possible care whether or not they take part.

If you decide you want your child 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 your child taking part in the research project
- Consent for your child to have the tests and treatments that are described
- Consent to the use of your child's 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 and 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 rTMS can be used to improve social function. rTMS is a safe and non-invasive means of stimulating nerve cells in a particular part of the brain via the administration of brief magnetic pulses. rTMS has been developed as a treatment for major depressive disorder, and we have previously found that rTMS can benefit social aspects of ASD.

In this study we will stimulate a region of the brain that is involved in social understanding and social communication. This region is called the right temporoparietal junction, or rTPJ.

Some participants will receive the real form of rTMS, while others will receive a sham or placebo form. The sham or placebo form mimics the feeling of rTMS, but no brain stimulation is delivered. You will not know which one your child receives until the end of your involvement in the study. Those who received the sham or placebo form will be given the opportunity to undergo the real rTMS treatment at the end of their involvement in the study.

150 people (aged 14-40 years) will take part in this study, which is being conducted throughout Australia. There are sites in Brisbane, Sydney, Melbourne, Adelaide, and Perth. Participants will be recruited from around Australia, but primarily the greater metropolitan regions within these five cities.

rTMS 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, Prof. Peter Enticott (Deakin University, Melbourne). This research has been funded by the National Health and Medical Research Council (NHMRC) of Australian through a Medical Research Future Fund grant (MRFF RCRDUN Neurological Disorders 2020; Application APP1199298).

3 What does participation in this research involve?

Your child will be participating in a randomised controlled research project. Sometimes we do not know which treatment is best for treating a condition. To find out we need to compare different treatments. We put people into groups and give each group a different treatment (in this case, real RTMS vs. sham/placebo RTMS). The results are compared to see if one is better. To try to make sure the groups are the same, each participant is put into a group by chance (random).

This is a double-blind study. This means that it will not be known which of the treatments your child is receiving (in this case, real rTMS or sham/placebo rTMS); the study doctor will also not know. However, in certain circumstances your study doctor can find out which treatment your child is receiving. Participants will be randomly allocated to either the real rTMS or sham/placebo RTMS condition. As mentioned, those allocated to the sham or placebo form will be given the opportunity to undergo the real rTMS treatment at the end of their involvement in the study.

This research project has been designed to make sure the researchers interpret the results in a fair and appropriate way and avoids study doctors or participants jumping to conclusions.

If you decide that your child can participate in this research project, you and your child will be asked to take part in a number of interviews and procedures over the course of approximately eight months. These are outlined below. You (or another parent/guardian of the child) must attend each session with your child.

Prior to completing the study, we will need to determine your child's eligibility to take part in the study. We will do this by asking you questions (either over the phone or via email) about their health. We will also ask you to provide a letter or report confirming your child's diagnosis of ASD; if you are not able to provide this, we will seek permission (via the consent form) to contact your child's doctor or psychologist directly to confirm their diagnosis.

Assessment Session One: The first assessment will take place at [site-specific location]. It will take approximately three hours, but your child will be given regular breaks throughout the session.

We will begin by asking you some questions about your child's health, which will help to confirm their eligibility to take part in the study. We will then ask you some questions about your child that are relevant to ASD. This will include, for example, what they enjoy doing and how much they like being with other people.

Your child will complete a short cognitive assessment, which involves solving puzzles and describing what different words mean.

Finally, your child will undergo electroencephalography (EEG), which involves wearing an "electrode cap" to measure the electrical activity of their brain, or their "brainwaves." The electrode cap feels similar to a swimming cap. It will also feel a little damp, as we need to put a small amount of gel or saline into the cap to ensure that we get accurate recordings. For most of the EEG your child will simply rest while sitting in a chair, but your child will also complete a short task on a computer that involves looking at different objects (e.g., faces, household furniture, butterflies).

Assessment Session Two: Around one-week after "Assessment Session One" your child will then undergo a magnetic resonance imaging (MRI) brain scan at [site-specific location]. The MRI brain scan takes around 45-60 minutes, during which they will be asked to lie still in an MRI scanner. (Please note that with preparation time you attend the MRI facility for up to two hours.) MRI is a routinely performed, painless ways of examining brain structure and activity. We will use the MRI to accurately place the rTMS device and ensure that we are stimulating the correct brain region. The MRI procedure may also help us better understand how the treatment works and to determine who is likely to respond to treatment and why.

Assessment Session Three: During the same week of "Assessment Session Two," you and your child will attend a two-hour assessment session at [site-specific location]. Here we will ask you questions about your child, some of which are relevant to ASD, while others relate to their concentration and behaviour. Your child will also be asked some questions about their mood, stress, and satisfaction with life. We will also ask your child to complete some cognitive tasks on a computer/tablet. These tasks measure their memory, attention, and understanding of other people's emotions. We will also ask your child to provide a sample for genetic analysis; this will involve them having a cotton swab rubbed against the inside of their cheek. These genetic analyses are conducted to investigate whether people with certain genetic profiles respond better to the intervention. You will not receive any health information from these genetic analyses, and they are not considered to be clinically informative.

rTMS Intervention (4 weeks): The week after "Assessment Session Three" your child will begin the rTMS intervention, which involves attending [site-specific location] and receiving rTMS

for 3 minutes, 20 seconds each consecutive weekday for a four-week period (20 RTMS sessions in total).

Your child will have their first rTMS session on the Monday after "Assessment Session Three." At the beginning of the first session we will administer transcranial magnetic stimulation (TMS) to the area of the brain that controls the muscles in their hand. This will measure how excitable their brain is and is used to help us determine the personalised settings that will be used for their rTMS treatments. This takes approximately 10 minutes and is not uncomfortable, although they may feel some twitches in the muscle of their hand while the TMS is occurring.

During each rTMS session your child will be awake, alert, and aware of what is happening at all times. During rTMS a coil will be placed against their head, through which rTMS 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 sensations associated with rTMS are mild, and most people describe it as a "tapping" sensation on their head. During an rTMS procedure, your child will hear clicking sounds as the current passes through the coil. Your child will wear earplugs so that this noise doesn't disturb them.

Including setup time, each subsequent treatment session should only take approximately 10 minutes. At the end of each treatment week (i.e., on the Friday session) we will ask you and your child a number of questions about their experience of RTMS, and whether you feel that they have experienced any side effects.

Assessment Session Four: The week after your child's last RTMS session, you and your child will attend another two-hour assessment session at [site-specific location]. Here we will again ask you questions about your child, some of which are relevant to ASD, while others relate to their concentration and behaviour. Your child will also be asked some questions about their mood, stress, and satisfaction with life. We will also again ask your child to complete some cognitive tasks on a computer/tablet and to provide another sample (cheek swab) for genetic analysis.

Assessment Session Five: One-month after your child's last RTMS session, you and your child will attend another two-hour assessment session at [site-specific location]. This session will be identical to Assessment Session Four.

Assessment Session Six: Three-months after your child's last RTMS session, you and your child will attend a one-hour assessment session at [site-specific location]. This session will be identical to Assessment Session Five except that your child will not complete the computerised cognitive tasks.

Assessment Session Seven: Six-months after your child's last RTMS session, you and your child will attend a final two-hour assessment session at [site-specific location]. This session will be identical to Assessment Session Four. Following the assessment you will be unblinded; that is, a member of the research team will tell you and your child which treatment condition your child received (i.e., real or sham/placebo). If your child received the real treatment, you and your child's involvement in the study will conclude. If your child received the sham/placebo condition, your child will be given the opportunity to receive the real treatment. You can liaise with research staff to determine when you would like your child to undergo this four-week treatment.

There are no costs associated with participating in this research project. All treatments, tests, and medical care required as part of the research project will be provided to your child free of charge.

You will not be paid for you and your child's participation in this research, but you will be reimbursed $200 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 decide 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.

It is desirable that your child's local doctor be advised of your decision for your child to participate in this research project. If you have a local doctor, we strongly recommend that you inform them of your child's participation in this research project.

The research will be monitored by an independent Data Safety Monitoring Board, who will meet twice per year and review the conduct of the trial, monitor study data, and review any serious adverse events that might arise throughout the trial.

4 What does the child have to do?

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

There are several reasons why your child 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, or evidence of significant seizure activity as assessed by EEG
- 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)
- Being deemed unsuitable to undergo MRI (e.g., due to presence of metal in the body)
- Unstable medical condition
- Unstable medication regime
- Certain medications
- Substance use disorder
- Undergoing another current treatment for social communication
- Employment as a professional driver or machine operator (as the event of a seizure may affect employment)
- Pregnancy (female participants for whom child-bearing is a possibility will be required to undergo a urine screen)
- Certain neurological or psychiatric diagnoses (i.e., those not commonly associated with ASD, such as psychosis)
- A measured verbal intelligence quotient (IQ) of less than 55

5 Other relevant information about the research project

This study is only taking place in Australia. There will be 150 participants in this study, with 30 taking part in each of the five cities involved: Brisbane, Sydney, Melbourne, Adelaide, and Perth. There are a total of 14 organisations involved, including Universities, hospitals, and medical centres. This study is a follow-on study from our previous trials of rTMS in ASD, which have taken place at Monash University, Deakin University, The Alfred hospital, and the Epworth Camberwell.

6 Does the child have to take part in this research project?

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

If you do decide that the child can take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep. If your child has the capacity to provide informed consent, they may also sign the consent form.

Your decision that the child can or cannot take part, or that they can take part and then be withdrawn, will not affect their routine treatment, relationship with those treating them, or their relationship with *[site-specific Institution/s]*.

7 What are the possible benefits of taking part?

We cannot guarantee or promise that your child will receive any benefits from this research; however, possible benefits 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?

Repetitive Transcranial Magnetic Stimulation (rTMS)

Medical treatments often cause side effects. Your child may have none, some, or all of the effects listed below, and they may be mild, moderate, or severe. If your child has any of these side effects, or you are worried about them, talk with your study doctor. Your child's 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 your child gets.

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 child's treatment. The child's study doctor will discuss the best way of managing any side effects with you.

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

Headache: A headache can occur during rTMS and is thought to affect approximately 3% or 3 in 100 participants. It is thought to be caused by stimulation of nerves in the scalp. If your child were to experience such a headache, it will respond quickly to simple pain medication such as aspirin, ibuprofen, or paracetamol.

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

Seizure: The main concern associated with rTMS 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 such individuals). If your child has ever experienced a seizure, or if their EEG shows evidence of epileptiform activity, they will not be able to take part in this study. Investigators using rTMS have developed safety guidelines to minimise the risk of seizure. The RTMS 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 your child has rTMS. Staff will monitor your child and know how to treat a seizure should one occur.

The effects of rTMS 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. Individuals must not participate in the research if they are pregnant or trying to become pregnant, or breast-feeding. If your child is female and child-bearing is a possibility, they will be required to undergo a urinal pregnancy test prior to commencing rTMS. This test will be processed by a female member of the research staff.

If a participant becomes pregnant whilst participating in the research project, they should advise research staff immediately. The researchers will withdraw them from the research project and advise on further medical attention should this be necessary. An individual must not continue in the research if they become pregnant.

The ability to drive or use public transport will not be impaired following rTMS.

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

Magnetic Resonance Imaging (MRI)

MRI stands for magnetic resonance imaging. An MRI scanner is a machine that uses electromagnetic radiation (radio waves) in a strong magnetic field to take clear pictures of the inside of the body. Electromagnetic radiation is not the same as ionising radiation used, for example, in X-rays. The pictures taken by the machine are called MRI scans.

There are no proven long-term risks related to MRI scans as used in this research project. MRI is considered to be safe when performed at a centre with appropriate procedures. However, the magnetic attraction for some metal objects can pose a safety risk, so it is important that metal objects are not taken into the scanner room.

We will thoroughly examine your child to make sure there is no reason for them not to have the scan. You must tell us if your child has metal implanted in their body, such as a pacemaker or metal pins.

The MRI scanner is shaped like a narrow tunnel. Foam cushioning and Velcro straps are used to keep your child's 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 your child has experienced claustrophobia in the past. The MRI scanner is noisy, so your child will wear ear plugs and headphones to reduce the noise. We will be able to see your child and communicate with them during the scanning, and they will be able to stop the machine at any time by pushing a button. If they become uncomfortable during the session, we can pause or stop the scanning.

The scans we are taking are for research purposes. They are not intended to be used like scans taken for a full clinical examination. The scans will not be used to help diagnose, treat, or manage a particular condition. A specialist will look at your child's MRI scans for features relevant to the research project. On rare occasions, the specialist may find an unusual feature that could have a significant risk to your child's health. If this happens, we will contact you to talk about the findings. We cannot guarantee that we will find any/all unusual features. There may be wider implications from abnormal findings (e.g., for future applications for some kinds of insurance).

Other

We will ask you and your child if they 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 them in legal proceedings or otherwise.

If you or your child become upset or distressed as a result of your participation in the research, the study doctor will be able to arrange for counselling or other appropriate support. Any counselling or support will be provided by qualified staff who are not members of the research project team. This counselling will be provided free of charge.

9 What will happen to the child's test samples?

You will be asked to provide additional consent for the collection of your child's tissue (i.e., cheek swab) during the research project. As noted, these samples are collected to allow us to investigate whether certain genetic profiles are associated with a better response to the rTMS intervention. We will only conduct these analyses at a group level. You will not receive any health information (e.g., genetic disease predisposition) from these genetic analyses, and they are not considered to be clinically informative. Your child's genetic material and information, where identified or potentially identifiable, will not be released for other uses without your prior consent, unless required by law.

Samples of your child's tissue obtained for the purpose of this research project will be transferred to the Institute for Molecular Bioscience, University of Queensland, who will charge a fee to the research team to recover some of the costs of storing and administering the tissue samples. The University of Queensland will not transfer or sell your child's samples to any third party.

10 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 child's study doctor will tell you about it and discuss with you whether you want your child to continue in the research project. If you decide to withdraw your child from the study, your child's study doctor will make arrangements for their regular health care to continue. If you decide to continue your child's involvement in the research project you will be asked to sign an updated consent form.

Also, on receiving new information, your child's study doctor might consider it to be in your child's best interests to withdraw them from the research project. If this happens, your child's study doctor will explain the reasons and arrange for your regular health care to continue.

11 Can the child have other treatments during this research project?

Whilst your child is participating in this research project, they can continue to take the medications or treatments they have been taking for their condition or for other reasons. It is important to tell the research staff about any treatments or medications your child is 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 child's participation in the research project.

Because this trial is assessing the effect of rTMS on social communication, your child cannot participate if they are also undergoing any other treatment or intervention for social communication. This includes interventions delivered by psychologists.

12 What if I withdraw the child from this research project?

If you decide to withdraw your child 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 for your child's participation during the research project, the study doctor and relevant study staff will not collect additional personal information from you or your child, 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 up to the time you withdraw your child will form part of the research project results. If you do not want them to do this, you must tell the researchers before your child joins the research project.

13 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 drug/treatment/device being shown not to be effective
- The drug/treatment/device being shown to work and not need further testing
- Decisions made by local regulatory/health authorities.

14 What happens when the research project ends?

You will be sent a summary of the main findings when the project has been completed. This is a 4-year study and it is expected that study results will be available by late 2024. Your child's data will then be securely archived at Deakin University.

Please note that RTMS will not be available from the research sites after completing the study. It may be approved for future use in ASD, but this will depend on the results from the current study.

Part 2 How is the research project being conducted?

15 What will happen to information about my child?

By signing the consent form, you consent to the study doctor and relevant research staff collecting and using personal information about your child for the research project. Any information obtained in connection with this research project that can identify your child will remain confidential. Upon enrolment in the trial your child will be allocated a unique study identification code. Your child's name will not appear with the research data that we collect from you and them, and it will only be possible to re-identify your child's data using the study code. Only the research team will know which code identifies which participant. Your child's information will only be used for the purpose of this research project and future research projects, and it will only be disclosed with your permission, except as required by law.

Information about your child may be obtained from your child's health records held at this and other health services for the purpose of this research. By signing the consent form, you agree to the study team accessing your child's health records if they are relevant to your child's participation in this research project.

Your child's health records and any information obtained during the research project are subject to inspection (for the purpose of verifying the procedures and the data) by the relevant authorities and authorised representatives of the Sponsor, Deakin University, the institution relevant to this Participant Information Sheet, *[Name of institution]*, or as required by law. By signing the Consent Form, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

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 your child cannot be identified, except with your permission. We will only present

group-level findings (e.g., average scores across the group) and no individual data will be reported.

In accordance with relevant Australian *and/or [Name of state/territory]* privacy and other relevant laws, you have the right to request access to your child's 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 child's information.

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

It is expected that deidentified data from this study will be made available to other researchers via online data repositories. Your child will not be able to be identified in these repositories. It is also possible that the research team will use your child's data from this research project for future studies, but again they will not be able to be identified.

16 Complaints and compensation

If your child 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.

If you have complaints about you or your child's treatment by members of staff working on this research project, you should contact the person nominated in Section 19 below. If you have complaints about any of the ethical aspects of this study, you can contact the local reviewing HREC Executive Officer nominated in Section 19 below. Complaints about clinical trials can also be directed to the Office of the Australian Information Commissioner.

17 Who is organising and funding the research?

This research project is being conducted by a team of researchers led by Prof. Peter Enticott from Deakin University, Victoria. It is funded through a Medical Research Future Fund grant from the National Health and Medical Research Council to Prof. Enticott and the research team.

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

18 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 HREC of Monash Health and *[Name of institutions]*.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2018)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

19 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 your child has any medical problems that may be related to their involvement in the project (for example, any side effects),

you can contact your site's principal study doctor on *[phone number]* or any of the following people:

Study contact person

Name	*[Name]*
Position	*[Position]*
Telephone	*[Phone number]*
Email	*[Email address]*

Clinical contact person

Name	*[Name]*
Position	*[Position]*
Telephone	*[Phone number]*
Email	*[Email address]*

For matters relating to research at the site at which you are participating, the details of the local site complaints person are:

Complaints contact person

Name	*[Name]*
Position	*[Position]*
Telephone	*[Phone number]*
Email	*[Email address]*

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 approving this research and HREC Executive Officer details

Reviewing HREC name	*Monash Health*
HREC Executive Officer	*Ms Deborah Dell*
Telephone	*(03) 9594 4605*
Email	*research@monashhealth.org*

Local HREC Office contact (Single Site - Research Governance Officer)

Name	*[Name]*
Position	*[Position]*
Telephone	*[Phone number]*
Email	*[Email address]*

Consent Form - *Adult providing own consent*

Title	*Does repetitive transcranial magnetic stimulation (rTMS), compared to sham rTMS, improve social communication in adolescents and young adults with autism spectrum disorder (ASD)?*
Short Title	*MRFF RTMS-ASD*
Protocol Number	*v2, 11/09/2020*
Project Sponsor	*Deakin University*
Coordinating Principal Investigator	*Prof. Peter Enticott*
Associate Investigator(s)	*Prof. Paul Fitzgerald, A/Prof. Karen Barlow, Prof. Ian Hickie, Dr Melissa Licari, Dr Nigel Rogasch, Prof. Christel Middeldorp, Dr Scott Clark, Dr Ann-Maree Vallence, Dr Kelsie Boulton, Prof. Adam Guastella, Prof. Andrew Whitehouse, Prof. Cherrie Galletly, Dr Gail Alvares, Dr Hakuei Fujiyama, A/Prof. Helen Heussler, A/Prof. Jeffrey Craig, Dr Melissa Kirkovski, Dr Natalie Mills, Prof. Nicole Rinehart, Dr Peter Donaldson, Dr Talitha Ford, Prof. Karen Caeyenberghs*
Location	*[Location where the research will be conducted]*

Consent Agreement

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 the child's doctors, other health professionals, hospitals or laboratories outside this hospital to release information to *[Name of Institution]* concerning the child's 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 the child participating in this research project as described and understand that I am free to withdraw them at any time during the research project without affecting their future health care.

I freely agree to participate in this research project as described (e.g., completion of questionnaires) 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 agree for my child's anonymous study data to be shared with other researchers, including those outside *[Name of Institution]* and outside Australia, for future studies.

I agree to my child's anonymised data being made available through online repositories and to the use of my data in any future research.

Declaration by Parent/Guardian – for Parent/Guardian who has read the information

Name of Child (please print) _____

Name of Parent/Guardian (please print) _____

Signature of Parent/Guardian _____ Date _____

Declaration by Young Person – for participants under the age of 18 who have capacity to provide informed consent

Name of Young Person (please print) _____

Signature of Young Person _____ Date _____

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.

Continued on next page

I consent to the storage and use of tissue samples (cheek swabs) taken from my child for use, as described in the relevant section of the Participant Information Sheet, for:

- This specific research project
- Other research that is closely related to this research project
- Any future research.

By signing this consent section, I agree to the use of my child's tissue samples for genetic testing, as outlined in the relevant Section of the Participant Information Sheet.

Name of Child (please print) _____

Name of Parent/Guardian (please print) _____

Signature of Parent/Guardian _____ Date _____

Name of Young Person (please print) _____

Signature of Young Person _____ Date _____

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 - *Parent/Guardian consenting on behalf of participant*

Title	*Does repetitive transcranial magnetic stimulation (rTMS), compared to sham rTMS, improve social communication in adolescents and young adults with autism spectrum disorder (ASD)?*
Short Title	*MRFF RTMS-ASD*
Protocol Number	*v2, 11/09/2020*
Project Sponsor	*Deakin University*
Coordinating Principal Investigator	*Prof. Peter Enticott*
Associate Investigator(s)	*Prof. Paul Fitzgerald, A/Prof. Karen Barlow, Prof. Ian Hickie, Dr Melissa Licari, Dr Nigel Rogasch, Prof. Christel Middeldorp, Dr Scott Clark, Dr Ann-Maree Vallence, Dr Kelsie Boulton, Prof. Adam Guastella, Prof. Andrew Whitehouse, Prof. Cherrie Galletly, Dr Gail Alvares, Dr Hakuei Fujiyama, A/Prof. Helen Heussler, A/Prof. Jeffrey Craig, Dr Melissa Kirkovski, Dr Natalie Mills, Prof. Nicole Rinehart, Dr Peter Donaldson, Dr Talitha Ford, Prof. Karen Caeyenberghs*
Location *(where CPI/PI will recruit)*	*[Location where the research will be conducted]*

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 *[Institution]*.

Name of Child (please print) _____

Name of Parent/Guardian (please print) _____

Signature of Parent/Guardian _____ Date_____

Name of Young Person (please print) _____

Signature of Young Person _____ Date_____

Description of circumstances where communicated verbally:

Continued on next page

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.

BIOLOGICAL SPECIMENS

Participants will be administered a buccal swab on two occasions, which involves rubbing a cotton bud against the inside of the cheek. These will be collected in person by a member of the research team at each site. Specimens will then be sealed in a DNA/RNA Shield tube and labelled with the participant's unique study identification code. It will then be transported by courier/post to the Institute of Molecular Bioscience, University of Queensland, for extraction, storage, and analysis.

Numerical data arising from genetic and epigenetic analyses will be sent electronically to the research team (Chief Investigators Prof. Enticott and Prof. Middeldorp) and stored in REDCap databases. PDF files containing results will also be stored in REDCap.

The research team will retain all biospecimens, which will be securely stored at the Institute of Molecular Bioscience, University of Queensland. This will allow the possibility of future analyses, particularly to determine genetic and epigenetic factors associated with a clinical response to the TBS intervention. The research team may contribute results from these data to future collaborative projects, which may involve external researchers who are not involved in the current trial. No information that could identify a participant will be shared. Participants (and their parent/guardian where necessary) will be asked to provide permission for future biospecimen use as part of the informed consent procedure.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page Number on which item is reported
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	15
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	7, 13
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	7
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6-10
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	n/a
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	n/a
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8-9

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 1, 11-12
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8-9
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9-10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9-10
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	13
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	9

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	13
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Appendix
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	13
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13-14

	31b	Authorship eligibility guidelines and any intended use of professional writers	13
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	10, 14
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Appendix

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Repetitive transcranial magnetic stimulation (rTMS) in autism spectrum disorder: protocol for a multicentre randomised controlled clinical trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-046830.R1
Article Type:	Protocol
Date Submitted by the Author:	18-Apr-2021
Complete List of Authors:	Enticott, Peter; Deakin University School of Psychology Barlow, Karen; The University of Queensland Child Health Research Centre, Child Health Research Centre; Children's Health Queensland Hospital and Health Service Guastella, Adam; The University of Sydney Brain and Mind Centre, Clinical Research Unit Licari, Melissa; Telethon Kids Institute Rogasch, Nigel; The University of Adelaide Adelaide Medical School; South Australian Health and Medical Research Institute Middeldorp, Christel; The University of Queensland Child Health Research Centre; Children's Health Queensland Hospital and Health Service Clark, Scott; The University of Adelaide Adelaide Medical School Vallence, Ann-Maree; Murdoch University, School of Psychology and Exercise Sciences; Murdoch University, Centre for Molecular Medicine and Innovative Therapeutics Boulton, Kelsie; The University of Sydney Brain and Mind Centre Hickie, Ian; The University of Sydney Brain and Mind Centre, Brain and Mind Centre Whitehouse, Andrew; Telethon Kids Institute; Cooperative Research Centre for Living With Autism Galletly, Cherrie; The University of Adelaide Adelaide Medical School Alvares, Gail; Telethon Kids Institute Fujiyama, Hakuei; Murdoch University, School of Psychology and Exercise Sciences Heussler, Helen; The University of Queensland Child Health Research Centre, Child Development; Children's Health Queensland Hospital and Health Service, Centre fro Children's Health Research Craig, Jeffrey; Deakin University School of Medicine, School of Psychology Kirkovski, Melissa; Deakin University School of Psychology Mills, Natalie; The University of Adelaide Adelaide Medical School Rinehart, Nicole; Deakin University School of Psychology Donaldson, Peter; Deakin University School of Psychology Ford, Talitha; Deakin University School of Psychology Caeyenberghs, Karen; Deakin University School of Psychology, School of Psychology Albein-Urios, Natalia; Deakin University School of Psychology, School of Psychology Bekkali, Soukayna; Deakin University School of Psychology

	Fitzgerald , Paul; Monash University Central Clinical School; Epworth HealthCare, Epworth Centre for Innovation in Mental Health
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Mental health
Keywords:	Child & adolescent psychiatry < PSYCHIATRY, Developmental neurology & neurodisability < PAEDIATRICS, Paediatric neurology < PAEDIATRICS, Neurophysiology < NEUROLOGY

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Repetitive transcranial magnetic stimulation (rTMS) in autism spectrum disorder: protocol for a multicentre randomised controlled clinical trial

Peter G. Enticott*, School of Psychology, Deakin University, Geelong, Australia
Karen Barlow, Child Health Research Centre, The University of Queensland, South Brisbane, Australia; Children's Health Queensland Hospital and Health Service, Herston, Queensland
Adam J. Guastella, Brain and Mind Centre, University of Sydney, Camperdown, Australia
Melissa K. Licari, Research Fellow, Telethon Kids Institute, The University of Western Australia, Nedlands, Australia
Nigel C. Rogasch, Adelaide Medical School, The University of Adelaide, Adelaide, Australia; South Australian Health and Medical Research Institute (SAHMRI), Adelaide, Australia
Christel M. Middeldorp, Child Health Research Centre, The University of Queensland, South Brisbane, Australia; Children's Health Queensland Hospital and Health Service, Herston, Queensland
Scott R. Clark, Adelaide Medical School, The University of Adelaide, Adelaide, Australia
Ann-Maree Vallence, School of Psychology and Exercise Sciences, Murdoch University, Murdoch, Australia; Centre for Molecular Medicine and Innovative Therapeutics, Murdoch University, Australia
Kelsie A. Boulton, Brain and Mind Centre, University of Sydney, Camperdown, Australia
Ian B. Hickie, Brain and Mind Centre, University of Sydney, Camperdown, Australia Andrew J. O. Whitehouse, Telethon Kids Institute, The University of Western Australia, Nedlands, Australia; Cooperative Research Centre for Living with Autism, St Lucia, Queensland, Australia
Cherrie Galletly, Adelaide Medical School, The University of Adelaide, Adelaide, Australia
Gail Alvares, Telethon Kids Institute, The University of Western Australia, Nedlands, Australia
Hakuei Fujiyama, School of Psychology and Exercise Sciences, Murdoch University, Murdoch, Australia
Helen Heussler, Child Health Research Centre, The University of Queensland, South Brisbane, Australia; Children's Health Queensland Hospital and Health Service, Herston, Queensland
Jeffrey Craig, School of Medicine, Deakin University, Geelong, Australia
Melissa Kirkovski, School of Psychology, Deakin University, Geelong, Australia
Natalie T. Mills, Adelaide Medical School, The University of Adelaide, Adelaide, Australia
Nicole J. Rinehart, School of Psychology, Deakin University, Geelong, Australia
Peter H. Donaldson, School of Psychology, Deakin University, Geelong, Australia
Talitha C. Ford, School of Psychology, Deakin University, Geelong, Australia
Karen Caeyenberghs, School of Psychology, Deakin University, Geelong, Australia
Natalia Albein-Urios, School of Psychology, Deakin University, Geelong, Australia
Soukayna Bekkali, School of Psychology, Deakin University, Geelong, Australia
Paul B. Fitzgerald, Central Clinical School, Monash University; Epworth Centre for Innovation in Mental Health, Epworth HealthCare, Camberwell, Australia

Word count (excluding title page, abstract, references, figures and tables): 4,001

*Correspondence to: Peter G. Enticott, School of Psychology, Deakin University, 221 Burwood Hwy, Burwood, Victoria, 3125, Australia.
Email: peter.enticott@deakin.edu.au

v2, 13 April 2021

ABSTRACT

Introduction

There are no well-established biomedical treatments for the core symptoms of autism spectrum disorder (ASD). A small number of studies suggest that repetitive transcranial magnetic stimulation (rTMS), a non-invasive brain stimulation technique, may improve clinical and cognitive outcomes in ASD. We describe here the protocol for a funded multicentre randomised controlled clinical trial to investigate whether a course of rTMS to the right temporoparietal junction (rTPJ), which has demonstrated abnormal brain activation in ASD, can improve social communication in adolescents and young adults with ASD.

Methods and analysis

This study will evaluate the safety and efficacy of a four-week course of intermittent theta burst stimulation (iTBS, a variant of rTMS) in ASD. Participants meeting criteria for DSM-5 ASD (n = 150, aged 14-40 years) will receive 20 sessions of either active iTBS (600 pulses) or sham iTBS (in which a sham coil mimics the sensation of iTBS, but no active stimulation is delivered) to the rTPJ. Participants will undergo a range of clinical, cognitive, epi/genetic, and neurophysiological assessments before and at multiple time points up to six months after iTBS. Safety will be assessed via a structured questionnaire and adverse event reporting. The study will be conducted from November 2020 to October 2024.

Ethics and dissemination

The study was approved by the Human Research Ethics Committee of Monash Health (Melbourne, Australia) under Australia's National Mutual Acceptance scheme. The trial is registered (prospectively) at the Australian New Zealand Clinical Trials Registry (ANZCTR) ACTRN12620000890932p, will be conducted according to Good Clinical Practice, and findings will be written up for scholarly publication.

Strengths and limitations of this study

- This multisite randomised controlled trial will be the largest trial of rTMS in ASD to date
- rTMS will be applied to rTPJ, a cortical region that has demonstrated abnormal activation in ASD and forms a major hub of the "social brain" subnetwork
- Participants will undergo structural MRI scans, with rTMS coil position determined via individualised neuronavigation
- Adolescent and young adult participants will receive rTMS interventions as outpatients, and complete a comprehensive range of clinical, neuropsychological, and neurophysiological assessments
- A limitation of the study is the use of only a sham control condition, rather than an additional "active control" site to determine whether effects are specific to rTPJ (rather than a general effect of brain stimulation)

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that impacts a range of domains, including social communication, behaviour, cognition, emotion regulation, and sensorimotor function[1]. Core symptoms of ASD include social interaction and communication problems, and restricted and repetitive behaviours. Comorbid neurodevelopmental disorders (e.g., attention deficit hyperactivity disorder [ADHD]) and psychiatric disorders (e.g., depression, anxiety) are very common[2 3], with the latter often associated with the core social communicative difficulties[4 5].

Despite the high prevalence of ASD (1 in 59[6]), few clinical interventions target core symptoms beyond early-middle childhood. ASD diagnosis typically occurs by the age of 4-6 years[6], and early, intensive intervention throughout these years is associated with the best outcomes for individuals with ASD and their families[7]. Unfortunately, there is little clinical support available for adolescents and young adults with ASD, who often continue to experience social communication symptoms that result in barriers to education, employment, and community participation. As noted, this group also experiences extremely poor mental health that is much worse than the general population; for instance, lifetime depression and anxiety rates are estimated at 37% and 42%, respectively[2].

Non-invasive brain stimulation (NIBS) has emerged as a novel, safe, and efficacious intervention for a range of brain-based disorders. These techniques allow non-invasive modulation of specific brain regions via electromagnetic or electrical stimulation. The most common of these is repetitive transcranial magnetic stimulation (rTMS), which is now widely used as an intervention for treatment-resistant major depressive disorder[8]. It has also been established as an intervention for other neurological disorders, including migraine and obsessive-compulsive disorder[9 10].

rTMS is administered via a plastic-coated metallic coil that is held against the scalp. This coil emits focal, time-varying electromagnetic pulses, which induce electrical current in superficial cortical tissue, thus stimulating neurons in the local region. Depending on the frequency and strength of pulses administered, rTMS can be used to either enhance cortical excitability (i.e., upregulate neural activity), or decrease cortical excitability (i.e., downregulate neural activity) in the stimulated region. This is particularly useful when targeting regions (or nodes) of brain networks known to be either underactive or overactive in particular conditions. For instance, high-frequency (excitatory) rTMS has been used to stimulate underactive left dorsolateral prefrontal cortex (DLPFC) in treatment-resistant depression[11], while low-frequency (inhibitory) rTMS has been used to downregulate excessive activity in left auditory cortex in schizophrenia[12] and supplementary motor area (SMA) in Tourette's disorder[13]. Importantly, rTMS also influences broader brain networks that involve the stimulated region[14 15], and this is thought to contribute to its clinical efficacy. Here we will stimulate the right temporoparietal junction (rTPJ), a key node for social cognition, which is a typical area of difficulty among individuals with ASD [16].

The brain functions as a set of interconnected networks disseminating neuronal information across a broad range of distributed areas [17]. From a neurobiological perspective, ASD is commonly understood as a disorder of synaptic plasticity and neural connectivity, leading to

abnormalities in brain network connectivity between brain regions. These appear to be mediated by disruptions in both excitatory (e.g., glutamatergic) and inhibitory (e.g., GABAergic) processes[18 19]. There are also well-documented abnormalities in local "node" activity, particularly within networks that comprise the so-called "social brain," including rTPJ[20 21]. Indeed, the rTPJ shows consistent differences in activation between those with and without ASD[16 20-22], while meta-analysis demonstrates reduced rTPJ functional connectivity in ASD [23]. Accordingly, rTMS to this region has the potential to modulate local and regional brain activity within networks implicated in the core social symptoms of ASD.

rTMS is considered a very safe and tolerable technique. It is typically administered by an experienced clinician (nurse or physician), and patients are monitored throughout and at the completion of rTMS administration. Clinical researchers have established a detailed set of safety guidelines, and when rTMS is administered within guideline parameters serious adverse effects are exceedingly rare[24 25]. NIBS (including rTMS) is also considered very safe for paediatric populations, with a recent study showing no adverse effects across 382 children aged 0-18 years[26].

Previously, NIBS has been used to investigate the neuropathophysiology of ASD[27-30]. More recently, several research groups (including ours) have investigated whether rTMS could have clinical utility as an intervention in ASD., These studies (see systematic reviews[31-33]) indicate that: low-frequency stimulation of the DLPFC can reduce repetitive behaviours, improve neurophysiological markers of perception, and reduce irritability; low-frequency SMA stimulation can improve movement-related cortical potentials, and; low-frequency stimulation of the premotor cortex can improve sensorimotor integration. While promising, these studies are hampered by small sample sizes a lack of an appropriate control condition (placebo or sham stimulation), and moderate-to-high risk of bias[31].

At present, only two placebo-controlled randomised controlled trials (RCTs) have been conducted, both of which were double-blind. The first demonstrated that two weeks of daily, high-frequency rTMS to bilateral dorsomedial prefrontal cortex (dmPFC), compared to sham rTMS, improved self-report social relating symptoms in adults with ASD (n = 28) one-month after intervention completion[34]. A recent study demonstrated that four weeks of high-frequency stimulation of bilateral DLPFC did not improve executive function in adolescents and young adults with ASD (n = 40)[35]. There was, however, evidence for a beneficial effect of rTMS for those with lower adaptive functioning at baseline. While providing preliminary, placebo-controlled support for rTMS in ASD, these studies are limited by small sample size.

Rationale/Justification

A recent international "consensus statement" provides recommendations for future rTMS research in ASD[36]. Considering the clinical heterogeneity of ASD, there is agreement that "large, multisite, double-blind, placebo-controlled trials with carefully selected neurobiological targets and outcome measures" are required. It is also necessary to understand variability in the response to rTMS that can lead to an individualised therapeutic approach (i.e., personalised medicine approach). These include demographic (e.g., age, sex), clinical (e.g., disorder severity, cognitive/symptom profile), neurobiological (e.g., cortical

thickness, structural and functional connectivity), and genetic/epigenetic factors. Accordingly, we will conduct a large-scale, multi-site investigation of the safety and efficacy of rTMS in ASD that involves (a) feasible and tolerable stimulation paradigms, (b) a carefully selected neurobiological target and mode of stimulation, and (c) rigorous methodological approaches, including individualised stereotactic neuronavigation, an appropriate control condition, and efficacious double blinding. If successful, this trial will establish a first biomedical intervention to improve social communicative symptoms in adolescents and young adults diagnosed with ASD, and inform on factors associated with intervention response, with anticipated benefits in mental health, quality of life, and social participation.

Research Hypotheses

In ASD, active rTMS to rTPJ, when compared to sham rTMS, will be associated with:

1. Improved social communication, measured using the Social Responsiveness Scale – 2nd Edition (SRS-2) (evident one-month after end of rTMS, maintained at three- and six-months) (primary outcome);
2. Improved social cognitive performance, measured using face processing/face emotion processing neuropsychological tasks (evident immediately after rTMS, maintained at one-, three-, and six-months);
3. Improved quality of life, measured using the Personal Wellbeing Index (evident one-month after rTMS, maintained at three- and six-months);
4. Acceptable tolerability and safety (as measured by a structured interview and adverse event reporting).

METHODS AND ANALYSIS

Study Design and Participants

This is a four-year multicentre Australian study to assess the safety and efficacy of a four-week course of rTMS to improve social communication in adolescents and young adults diagnosed with ASD. It will be a parallel group (between-subjects), double-blind, placebo-controlled RCT. Participants will be 150 individuals meeting criteria for DSM-5[1] ASD and aged between 14-40 years. While broad, this age range was selected to ensure the feasibility of participant recruitment and to target age groups (i.e., adolescents and young adults) where interventions for ASD are lacking. They will be recruited through existing research participant databases, the Australian Autism Biobank[37], and advertisements in local clinics, advocacy/support groups, and via social media. The research team will also engage popular media, both locally and nationally, to promote recruitment.

The study will be overseen by a Research Management Group, which comprises the ten Chief Investigators, Study Coordinator, and Site Coordinators. They will meet monthly via videoconference for the duration of the trial. There will be 30 participants enrolled at each of the cities involved (Brisbane, Sydney, Melbourne, Adelaide, Perth). Participants will undergo 20 intervention sessions (one per weekday for four consecutive weeks) of either active or sham (i.e., placebo) rTMS. Participants will be assessed before and up to 6 months after intervention and in accordance with Good Clinical Practice (GCP). Assessments will

evaluate social communication, neuropsychological function, quality of life, safety, and tolerability. There will be five primary intervention sites within Australia (Brisbane, Sydney, Melbourne, Adelaide, Perth) and additional local sites to support recruitment, assessment, genetic analysis, and neuroimaging. These will include both University and hospital sites. Written informed consent will be obtained from participants (or their parent/guardian in the case of minors, aged 14-17 years) by a local Chief Investigator or Site Coordinator. Model participant Information and consent forms for parents/guardians and adult participants are provided as Supplemental Material.

Patient and Public Involvement

The research team have engaged in extensive consultation with community groups in recent years, including multiple community forums on rTMS). We have also consulted with autism organisations when preparing advertisements and other study-related communications. While participants were not directly involved in the design of this specific trial, throughout the study we will engage a range of community and advocacy groups in the implementation of the research, and health service partners to ensure rapid translation of our research findings to clinical practice. For instance, the Telethon Kids Institute (Western Australia) have established a community reference group with whom they regularly consult for consumer involvement, and this group will also be engaged for the current trial.

rTMS Protocol

Participants will receive standard intermittent theta burst stimulation (iTBS) to the rTPJ each consecutive weekday for a four-week period (20 sessions). iTBS was chosen as it is an "excitatory" paradigm that has the potential to target the reduced activation and connectivity commonly seen in rTPJ in ASD [16 20 21 23]. It can also be administered quickly and at a low intensity, which are important considerations in this clinical population. Participants will undergo either active iTBS or sham iTBS, where a "sham coil" is used to mimic the appearance, sound, and sensation of rTMS, but without delivering electromagnetic stimulation.

Participants will undergo 3T T1 magnetic resonance imaging (MRI) prior to the first rTMS session, and stereotactic neuronavigation will be used to determine the site of stimulation (MNI coordinates x = 56, y = -56, z = 18; see Figure 1).

All stimulation will be administered via a Magstim Rapid^2 stimulator (The Magstim Company Ltd., Wales, UK). A staff member trained in rTMS will deliver all rTMS interventions. A visual resting motor threshold (i.e., visual observation of muscle activation following TMS pulse) will be determined at the right hemisphere/left hand prior to the first rTMS session. Each iTBS is delivered with the following stimulation parameters:

- Burst pattern: 3 pulses delivered at 50 Hz
- Train duration: Bursts repeated 5 times per second (5 Hz) for 2 seconds (10 bursts)
- Intensity: 70% of resting motor threshold
- Inter-train interval: 8 seconds
- Total time: 200 seconds (3 minutes, 20 seconds)

- Total trains: 20
- Total bursts: 200
- Total pulses: 600

<<Insert Figure 1 around here>>

Figure 1. Site of rTMS coil localisation (MNI coordinates x = 56, y = -56, z = 18)

All rTMS procedures, including resting motor threshold, will be administered by a TMS clinician who is not blinded to study condition. Participants will be monitored by study staff for at least five minutes after each intervention session. They can then leave the facility and go about their normal daily activities, including driving. The participant will be administered the Non-invasive Brain Stimulation Post-Stimulation Interview at the end of each week of rTMS intervention (i.e., after the Friday session) to determine the presence/intensity of any side-effects. For child participants (aged 14-17 years), this interview will be conducted with both the parent/guardian and the child. Participants will also be regularly asked about their wellbeing during and immediately after each rTMS session. Any side effects reported in this manner will be documented in the participant's file and will be examined at the completion of the trial.

Inclusion and Exclusion Criteria

Inclusion Criteria

- Aged 14-40 years
- Meets criteria for ASD based on DSM-5 criteria (clinician reported), and confirmed via Autism Diagnostic Observation Schedule – Second Edition (ADOS-2)
- English-language fluency/proficiency

Exclusion Criteria

- History of seizure/s or epilepsy
- History of severe (traumatic) brain injury
- Contraindication to MRI (e.g., claustrophobia, metal implants)
- Formal verbal intelligence quotient VIQ assessment <55, as determined by Wechsler Abbreviated Scale of Intelligence (WASI-2)
- Comorbid neurological or psychiatric diagnosis not commonly associated with ASD (e.g., psychosis)
- Unstable medical condition
- Unstable medication regimen, or medication contraindicated for TMS
- Pregnancy or current breastfeeding
- Substance use/abuse disorder
- Concurrent intervention targeting social communication
- Evidence of significant epileptiform activity on electroencephalogram (EEG) (e.g., seizures on EEG, runs of epileptiform discharges)

Outcome Measures

Data collection and study timings are presented in Table 1. Participants are assessed prior to rTMS (T0), and at four points after rTMS: T1 (immediately after rTMS), T2 (one-month after

completion of rTMS), T3 (three-months after completion of rTMS), and T4 (six-months after completion of rTMS).

The primary outcome measure is the Social Responsiveness Scale – 2nd Edition (SRS-2; School-Age AutoScore Form for Parent/Guardian [parent/guardian report]/Adult AutoScore Form for Informant [informant report]) Total T-score, while the primary outcome point will be at 1-month after completion of rTMS (T2) compared with pre-rTMS (T0). For adult participants, an informant (parent/relative/friend) will complete the SRS-2 with respect to the participant.

Secondary outcomes encompass a range of clinical, neuropsychological, neurophysiological, and biological measures. Clinical measures include: Conners 3 (parent/guardian report)/Conners Adult ADHD Rating Scales (CAARS) (informant report and adult self-report); Aberrant Behaviour Checklist – Second Edition (ABC-2) (parent/guardian/informant report); Behaviour Rating Scale of Executive Function, Second Edition (BRIEF)/ Behaviour Rating Scale of Executive Function – Adult Version (BRIEF-A) (parent/guardian/informant report and adult self-report); World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) (parent/guardian/informant report); Depression, Anxiety and Stress Scale (DASS) (self-report); and Personal Wellbeing Index (PWI) (self-report).

Neuropsychological measures include: Reading the Mind in the Eyes Test (RMET); Benton Facial Recognition Test (BFRT); Cambridge Face Memory Test (CFMT); NIH Cognition Toolbox; and Working Memory Assessment.

Neurophysiological measures include: resting-state electroencephalography (EEG); and face processing event-related potentials (ERP).

The neuropsychological and neurophysiological measures were selected as they are associated with activation of the target cortical region (e.g., [38]); while there were additional paradigms that could have been used (e.g., biological motion processing), we were mindful of not overburdening our participants, and selected those that we felt most relevant to our social communication target.

Finally, a buccal swab will be administered both before and after the course of rTMS, which will allow an investigation of genetic and epigenetic predictors of intervention response, and potential epigenetic changes following rTMS.

The various electrophysiological and genetic measures that are being collected are highly exploratory but may help us to understand mechanisms by which rTMS exerts an influence on social communication.

<<Insert Table 1 around here>>

Randomisation

There will be an equal number of participants allocated to each condition at each of the five project sites (15 active, 15 sham; total 75 active, 75 sham). A computerised adaptive

randomisation procedure (minimisation method) will be performed, adjusting for baseline characteristics (age, sex, SRS T0 score)[39], which ensures a balance of conditions across trial sites. Randomisation will be completed by the Chief Investigator, who will provide this information to the intervention clinicians (who are not blinded) via email.

Statistical Analysis and Data Management

With respect to statistical power, allowing for 10% attrition of our 150 participants, and based on the estimated effect size from our previously published RCT (which revealed a moderate effect of rTMS[34]), a sample size of n = 135 in a mixed-model (2 groups, 5 time-points) will yield power of 0.99 (f = .20, α = 0.01). While this sample size is larger than the minimum suggested by a priori power analysis (n = 64, based on f = .20, α = 0.01, Power = 0.95), this will enable exploratory analysis to determine demographic, clinical, neuroimaging, and genetic predictors of treatment response.

Upon enrolment, participants will be allocated a unique study identification code. Their name will not appear with the research data collected. All data will be stored in REDCap[40] and on secure network locations governed by Deakin University. All Chief Investigators will have access to the final trial dataset. Any information obtained in connection with this research project that can identify a participant will remain confidential. Where a participant elects to withdraw from the study, we will retain and use any data collected prior to withdrawal.

Random effects linear mixed models will be used to ensure the inclusion of participants who have missing data, including those that withdraw from the study. Specifically, this will involve a between-subjects factor (rTMS condition: active vs. placebo) and a within-subjects factor (time of assessment: pre vs. post vs. one-month vs. three-months vs. six-months), with participant and site entered as random effects. We will employ an intention to treat (ITT) framework for these analyses. We will examine rTMS safety by exploring descriptive statistics arising from the structured questionnaire related to the development of possible side-effects. An interim analysis will be performed at the mid-point of data collection for possible trial futility. The above-mentioned a priori power analysis, where n = 64 is required to detect a moderate effect, suggests that we will be sufficiently powered to detect an effect of rTMS in this interim analysis.

Exploratory analyses will be undertaken to investigate factors, including genetic variants and structural/functional neuroimaging (e.g., diffusion MRI, resting-state functional MRI), that influence intervention response, and to investigate epigenetic changes following rTMS. We will use linear mixed models to determine the effect of rTMS on SRS-2 score, but with additional independent variables (e.g., age, sex, cognitive ability, ADOS-2 symptom severity, rTPJ structural and functional connectivity within the social brain subnetwork, polygenic risk score [PRS] for ASD[41]).

Epigenetic variation refers to variation in chromatin structure, which is associated with variation in gene expression. In contrast to DNA, epigenetic variation can change over time, for example following treatment[42]. Accordingly, we will compare epigenetic variation for DNA samples collected before and after rTMS and investigate any associations with

intervention response. (See Supplemental Material for a statement on Biological Specimens.)

At the conclusion of the project, all electronic and hard copy data will be archived within Deakin University (Information and Records Services). Electronic data will be retained on secure Deakin University servers and archived in REDCap, but also transferred to physical hard drives for archival storage. As some hard copy data will be stored at each site (e.g., signed consent forms, clinical files used during rTMS intervention), these will be securely couriered to Deakin University for archiving. Each site will be required to delete any electronic data that may remain at their site. As this is a clinical trial involving child participants, data will be retained indefinitely. Any published work from this study will be accompanied by publicly available deidentified data through the Open Science Framework (osf.io). The research team, including both Chief Investigators and Associate Investigators, all have the opportunity to conduct secondary analyses. This will be negotiated with the trial's Research Management Group, which comprises the ten Chief Investigators. Data may also be shared with external (national and international) collaborators to obtain larger sample sizes, which are often necessary to achieve the statistical power necessary to analyse biomarker data. This could include specific research projects or online data repositories, which may be accessed and used by external researchers.

Blinding

This is a double-blind study; accordingly, participants (and their parents/guardians, where relevant) and the testing researchers/statisticians will be blinded to intervention condition. The individual administering rTMS must select the appropriate coil (i.e., active or sham) and will therefore not be blinded, but this individual will not conduct any of the assessment or be involved in the statistical analyses. Unblinding may occur in the event of an adverse event. We will assess blinding integrity by asking participants to indicate, at the end of their four-week intervention, which condition they believed they received and the confidence (on an 11-point scale) in this judgment. At the conclusion of the final assessment (T4), participants will be unblinded as to their intervention condition by a member of the research team who is not blinded. Those who were allocated to the sham rTMS intervention will be offered the opportunity to undergo the real rTMS intervention. While this will occur after all assessments have been administered, scored, and entered into REDCap, we have developed standard operating procedures to minimise the likelihood that assessors will encounter participants completing the open label component.

Table 1.

Data Collection and Study Timings

Visits	Pre-enrolment	T0	Tx	T1	T2	T3	T4
Screening	X	X					
Written informed consent		X					
Randomisation		X					
Demographics	X	X					
Medical History	X	X					
Neuroimaging (MRI)		X					
Clinical EEG		X					
Buccal Swab		X		X			
ADOS-2		X					
WASI-2		X					
rTMS intervention (active/sham)			X				
NIBS:PSI			X				
SRS-2		X		X	X	X	X

Conners-3/CAARS	X	X	X	X	X
ABC-2	X	X	X	X	X
BRIEF/BRIEF-A	X	X	X	X	X
DASS	X	X	X	X	X
PWI	X	X	X	X	X
WHODAS 2.0	X	X	X	X	X
NIH Cognition Toolbox	X	X	X		X
RMET	X	X	X		X
BFRT	X	X	X		X
CFMT	X	X	X		X
Working Memory	X	X	X		X
rsEEG	X	X			
FP-ERP	X	X			

Notes: T0: Pre-rTMS; T1: week following rTMS; T2: one-month after completion of rTMS; T3: three-months after completion of rTMS; T4: six-months after completion of rTMS; MRI: magnetic resonance imaging; ADOS-2: Autism Diagnostic Observation Schedule, 2nd Edition; WASI-2: Wechsler Abbreviated Scale of Intelligence, 2nd Edition; rTMS: repetitive transcranial magnetic stimulation; NIBS:PSI: Non-invasive Brain Stimulation Post-stimulation Interview; SRS-2: Social Responsiveness Scale, 2nd Edition; CAARS: Conners Adult ADHD Rating Scales; ABC-2: Aberrant Behaviour Checklist, 2nd Edition; BRIEF: Brief Rating Inventory of Executive Function; BRIEF-A: Brief Rating Inventory of Executive Function – Adult Version; DASS: Depression Anxiety Stress Scale; PWI: Personal Wellbeing Index; WHODAS 2.0: World Health Organisation Disability Assessment Schedule; NIH: National Institutes of Health; RMET: Reading the Mind in the Eyes Test; BFRT: Benton Facial Recognition Test; CFMT: Cambridge Face Memory Test; rsEEG: resting-state electroencephalography; FP-ERP: face-processing event-related potentials.

Safety

Participants will undergo extensive screening to ensure that they meet safety criteria for undergoing rTMS[25]. For child participants, a parent or legal guardian will complete the screening. Participants will undergo EEG prior to their first rTMS session, and this will be reviewed by the trial neurologist. Any participants demonstrating evidence of runs of epileptiform discharges, as assessed by the study neurologist, will be withdrawn from the study. At the beginning of their first session, participants (or their parent/guardian for child participants) will again be screened to ensure that they can undergo rTMS.

A data safety monitoring board (DSMB) will be formed. This DSMB will comprise three senior clinical researchers independent to the current project. The DSMB will meet twice per year to review the conduct of the trial and monitor study data. They will also review any serious adverse events in a mid-trial safety analysis and on an *ad hoc* basis. Terms of reference will be based on advice from the National Health and Medical Research Council's Data Safety Monitoring Boards documentation.

Adverse events will be reported to the relevant Human Research Ethics Committees (HREC) immediately, and no later than 72 hours after the event. Depending on the nature and severity of the event, it may be necessary to also report to other regulatory bodies (e.g., Therapeutic Goods Administration) and suspend or terminate the trial. Should an individual suffer harm from trial participation, they will receive medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

ETHICS AND DISSEMINATION

This study has been approved by the Monash Health Human Research Ethics Committee (Melbourne, Australia; RES-20-0000-606A) under the National Mutual Acceptance scheme, which allows for mutual scientific and ethic acceptance across Australian jurisdictions and institutions. We will engage a range of community and advocacy groups in the implementation of the study, and health service partners to ensure rapid translation of our research findings to clinical practice.

The health outcomes of this study will be provided within 12 months of the trial's completion, initially through a freely accessible preprint and an open-access peer-reviewed journal publication. Authorship will be determined according to the standards outlined in the National Health and Medical Research Council's *Australian Code for the Responsible Conduct of Research*. Chief Investigators will also present the study findings at relevant scientific conferences and autism advocacy/support group community forums. The research team will also engage in more extensive public outreach and disseminate study findings widely through appropriate channels (e.g., study website, social media, news outlets). These dissemination pathways will also involve contributing to clinical guidelines (and direct engagement with healthcare providers).

Participants will be sent a plain language summary detailing the study results at the completion of the trial. This summary will be written as a lay summary and in a manner

accessible to participants and their families. A child version will also be sent to parents/guardians to share with their child. The summary will contain no identifying information and provide only group level results.

This project involves the collection of a large number of measures (e.g., clinical, neuropsychological, neuroimaging, genetic/epigenetic) and it is expected that the Chief Investigators will conduct further exploratory analyses on these data. This might include, for example, examining neuroimaging and genetic predictors of response to rTMS intervention and characterising epigenetic changes following rTMS.

TRIAL STATUS

At the time of submission recruitment has not commenced.

AUTHORS' CONTRIBUTIONS

PE, KB, AG, ML, NR, CM, SC, AV, KB, IH, CG, HF, HH, JC, MK, NM, PD, and PF contributed to the design of the study.
PE, KB, ML, NR, CM, SC, AV, KB, AW, GA, MK, PD, TF, KC, NA, SB, and PF contributed to the writing of the manuscript.
All authors approved the final draft of the manuscript.

FUNDING

This project has been funded by the National Health and Medical Research Council (NHMRC) under the Medical Research Future Fund (MRFF) Neurological Disorders 2020 scheme (Application ID: APP1199298).

PROJECT REGISTRATION

This project has been prospectively registered on the Australian New Zealand Clinical Trials Registry (ANZCTR; ACTRN12620000890932p).

COMPETING INTERESTS

There are no competing interests to declare.

TRIAL SPONSOR

Deakin University

Contact: Prof. Peter G. Enticott
221 Burwood Hwy, Burwood
Victoria, 3125, AUSTRALIA

ROLE OF SPONSOR AND STUDY

This is an investigator-initiated study funded by the Australian Government, who provided peer review but have had no other involvement in the trial.

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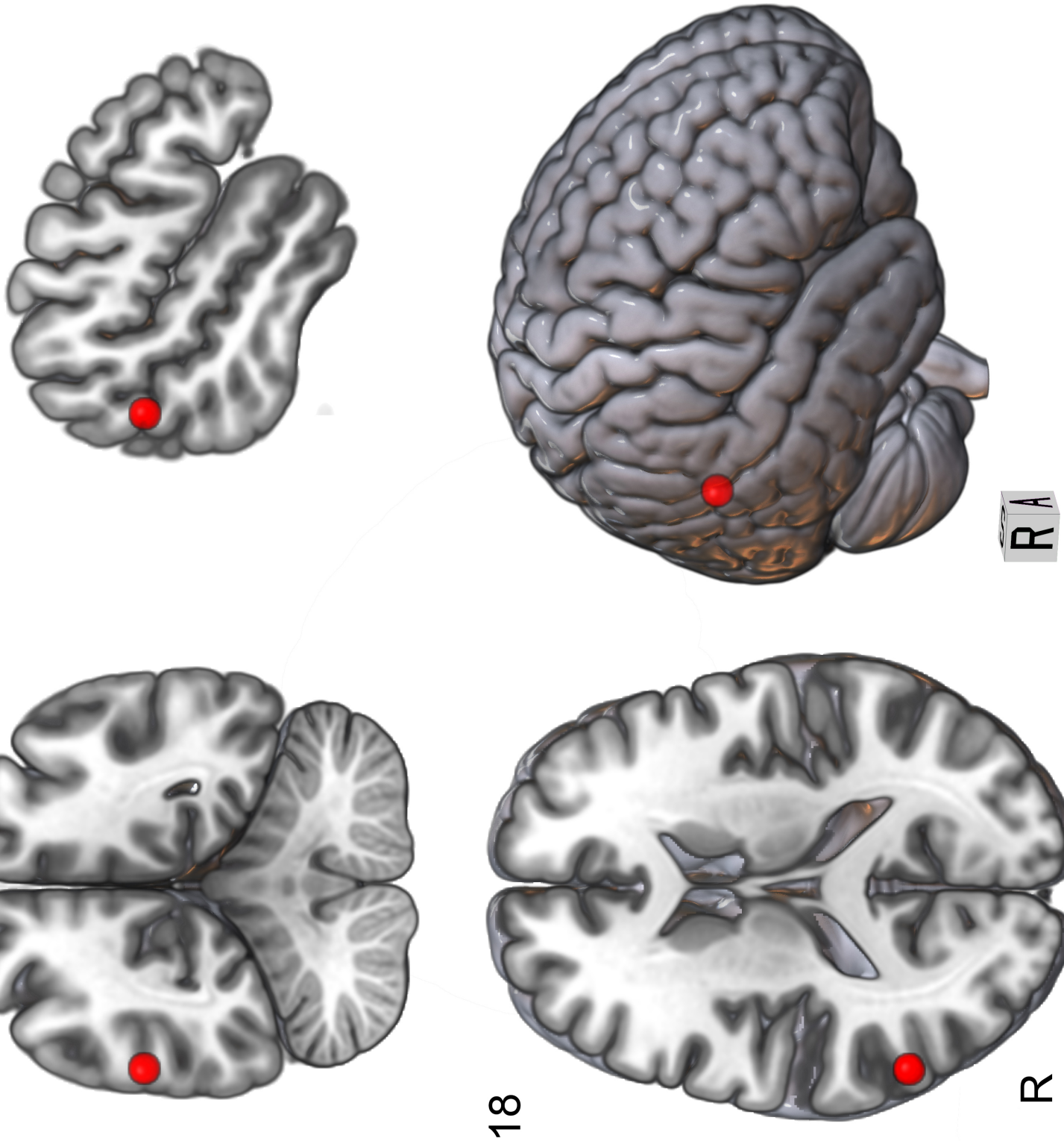
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Participant Information Sheet/Consent Form

Interventional Study - *Adult providing own consent*

[Insert site name]

Title	*Does repetitive transcranial magnetic stimulation (rTMS), compared to sham rTMS, improve social communication in adolescents and young adults with autism spectrum disorder (ASD)?*
Short Title	*MRFF TBS-ASD*
Protocol Number	*v2, 11/09/2020*
Project Sponsor	*Deakin University*
Coordinating Principal Investigator	*Prof. Peter Enticott*
Associate Investigator(s)	*Prof. Paul Fitzgerald, A/Prof. Karen Barlow, Prof. Ian Hickie, Dr Melissa Licari, Dr Nigel Rogasch, Prof. Christel Middeldorp, Dr Scott Clark, Dr Ann-Maree Vallence, Dr Kelsie Boulton, Prof. Adam Guastella, Prof. Andrew Whitehouse, Prof. Cherrie Galletly, Dr Gail Alvares, Dr Hakuei Fujiyama, A/Prof. Helen Heussler, A/Prof. Jeffrey Craig, Dr Melissa Kirkovski, Dr Natalie Mills, Prof. Nicole Rinehart, Dr Peter Donaldson, Dr Talitha Ford, Prof. Karen Caeyenberghs*
Location	*[Insert site-specific location]*

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 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 and 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 rTMS can be used to improve social function. rTMS is a safe and non-invasive means of stimulating nerve cells in a particular part of the brain via the administration of brief magnetic pulses. rTMS has been developed as a treatment for major depressive disorder, and we have previously found that rTMS can benefit social aspects of ASD.

In this study we will stimulate a region of the brain that is involved in social understanding and social communication. This region is called the right temporoparietal junction, or rTPJ.

Some participants will receive the real form of rTMS, while others will receive a sham or placebo form. The sham or placebo form mimics the feeling of rTMS, but no brain stimulation is delivered. You will not know which one you receive until the end of your involvement in the study. Those who received the sham or placebo form will be given the opportunity to undergo the real rTMS treatment at the end of their involvement in the study.

150 people (aged 14-40 years) will take part in this study, which is being conducted throughout Australia. There are sites in Brisbane, Sydney, Melbourne, Adelaide, and Perth. Participants will be recruited from around Australia, but primarily the greater metropolitan regions within these five cities.

rTMS 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, Prof. Peter Enticott (Deakin University, Melbourne). This research has been funded by the National Health and Medical Research Council (NHMRC) of Australian through a Medical Research Future Fund grant (MRFF RCRDUN Neurological Disorders 2020; Application APP1199298).

3 What does participation in this research involve?

You will be participating in a randomised controlled research project. Sometimes we do not know which treatment is best for treating a condition. To find out we need to compare different treatments. We put people into groups and give each group a different treatment (in this case, real rTMS vs. sham/placebo rTMS). The results are compared to see if one is better. To try to make sure the groups are the same, each participant is put into a group by chance (random).

This is a double-blind study. This means that neither you nor your study doctor will know which treatment you are receiving (in this case, real rTMS or sham/placebo rTMS). However, in certain circumstances your study doctor can find out which treatment you are receiving. Participants will be randomly allocated to either the real rTMS or sham/placebo rTMS condition. As mentioned, those allocated to the sham or placebo form will be given the opportunity to undergo the real rTMS treatment at the end of their involvement in the study.

This research project has been designed to make sure the researchers interpret the results in a fair and appropriate way and avoids study doctors or participants jumping to conclusions.

If you decide to take part in this project, you will be asked to take part in a number of interviews and procedures over the course of approximately eight months. These are outlined below.

Prior to completing the study, we will need to determine your eligibility to take part in the study. We will do this by asking you questions (either over the phone or via email) about your health. 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.

Assessment Session One: The first assessment will take place at [site-specific location]. It will take approximately three hours, but you will be given regular breaks throughout the session.

We will begin by asking you some questions about your health, which will help to confirm your eligibility to take part in the study. 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 (e.g., a parent, sibling, spouse, or close friend) complete a series of questionnaires. You can nominate this person and we will ask that they agree to complete these questionnaires now and another four times during the study.

You will then complete a short cognitive assessment, which involves solving puzzles and describing what different words mean.

Finally, you will undergo electroencephalography (EEG), which involves wearing an "electrode cap" to measure the electrical activity of your brain, or your "brainwaves." The electrode cap feels similar to a swimming cap. It will also feel a little damp, as we need to put a small amount of gel or saline into the cap to ensure that we get accurate recordings. For most of the EEG you will simply rest while sitting in a chair, but you will also complete a short task on a computer that involves looking at different objects (e.g., faces, household furniture, butterflies).

Assessment Session Two: Around one-week after "Assessment Session One" you will then undergo a magnetic resonance imaging (MRI) brain scan at [site-specific location]. The MRI brain scan takes around 45-60 minutes, during which you will be asked to lie still in an MRI scanner. (Please note that with preparation time you attend the MRI facility for up to two hours.) MRI is a routinely performed, painless ways of examining brain structure and activity. We will use the MRI to accurately place the rTMS device, and ensure that we are stimulating the correct brain region. The MRI procedure may also help us better understand how the treatment works and to determine who is likely to respond to treatment and why.

Assessment Session Three: During the same week of "Assessment Session Two," you will attend a two-hour assessment session at [site-specific location]. Here we will ask you questions about yourself, some of which are relevant to ASD, while others relate to your mood, concentration, stress, and your satisfaction with life. We will also ask you to complete some cognitive tasks on a computer/tablet. These tasks measure your memory, attention, and understanding of other people's emotions. We will also ask you to provide a sample for genetic analysis; this will involve having a cotton swab rubbed against the inside of your cheek. These genetic analyses are conducted to investigate whether people with certain genetic profiles respond better to the intervention. You will not receive any health information from these genetic analyses, and they are not considered to be clinically informative.

rTMS Intervention (4 weeks): The week after "Assessment Session Three" you will begin the rTMS intervention, which involves attending [site-specific location] and receiving rTMS for 3 minutes, 20 seconds each consecutive weekday for a four-week period (20 rTMS sessions in total).

You will have your first rTMS session on the Monday after "Assessment Session Three." At the beginning of the first session 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 rTMS treatments. 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.

During each rTMS session you will be awake, alert, and aware of what is happening at all times. During rTMS a coil will be placed against the head, through which rTMS 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 sensations associated with rTMS are mild, and most people describe it as a “tapping” sensation on their head. During a rTMS procedure you will hear clicking sounds as the current passes through the coil. You will wear earplugs so that this noise doesn’t disturb you.

Including setup time, each subsequent treatment session should only take approximately 10 minutes. At the end of each treatment week (i.e., on the Friday session) we will ask you a number of questions about your experience of RTMS, and whether you feel you have experienced any side effects.

Assessment Session Four: The week after your last rTMS session, you will attend another two-hour assessment session at [site-specific location]. Here we will again ask you questions about yourself, some of which are relevant to ASD, while others relate to your mood, concentration, stress, and satisfaction with life. We will also again ask you to complete some cognitive tasks on a computer/tablet and to provide another sample (cheek swab) for genetic analysis.

Assessment Session Five: One-month after your last rTMS session, you will attend another two-hour assessment session at [site-specific location]. This session will be identical to Assessment Session Four.

Assessment Session Six: Three-months after your last rTMS session, you will attend a one-hour assessment session at [site-specific location]. This session will be identical to Assessment Session Five except that you will not complete the computerised cognitive tasks.

Assessment Session Seven: Six-months after your last rTMS session, you will attend a final two-hour assessment session at [site-specific location]. This session will be identical to Assessment Session Five. Following the assessment, you will be unblinded; that is, a member of the research team will tell you which treatment condition you received (i.e., real or sham/placebo). If you received the real treatment, your involvement in the study will conclude. If you received the sham/placebo condition, you will be given the opportunity to receive the real treatment and can liaise with research staff to determine when you would like to undergo this four-week treatment.

There are no costs associated with participating in this research project. All treatments, tests, and medical care required as part of the research project will be provided to you free of charge.

You will not be paid for your participation in this research, but you will be reimbursed $200 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 decide 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.

It is desirable that your local doctor be advised of your decision to participate in this research project. If you have a local doctor, we strongly recommend that you inform them of your participation in this research project.

The research will be monitored by an independent Data Safety Monitoring Board, who will meet twice per year and review the conduct of the trial, monitor study data, and review any serious adverse events that might arise throughout the trial.

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, or evidence of significant seizure activity as assessed by EEG
- 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)
- Being deemed unsuitable to undergo MRI (e.g., due to presence of metal in the body)
- Unstable medical condition
- Unstable medication regime
- Certain medications
- Substance use disorder
- Undergoing another current treatment for social communication
- Employment as a professional driver or machine operator (as the event of a seizure may affect employment)
- Pregnancy (female participants for whom child-bearing is a possibility will be required to undergo a urine screen)
- Certain neurological or psychiatric diagnoses (i.e., those not commonly associated with ASD, such as psychosis)
- A measured verbal intelligence quotient (IQ) of less than 55

5 Other relevant information about the research project

This study is only taking place in Australia. There will be 150 participants in this study, with 30 taking part in each of the five cities involved: Brisbane, Sydney, Melbourne, Adelaide, and Perth. There are a total of 14 organisations involved, including Universities, hospitals, and medical centres. This study is a follow-on study from our previous trials of rTMS in ASD, which have taken place at Monash University, Deakin University, The Alfred hospital, and the Epworth Camberwell.

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 *[site-specific Institution/s]*.

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 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?

Repetitive Transcranial Magnetic Stimulation (rTMS)

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.

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 rTMS and is thought to affect approximately 3% or 3 in 100 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, ibuprofen, 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 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 such individuals). If you have ever experienced a seizure, or if your EEG shows evidence of epileptiform activity, 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 rTMS 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 rTMS. Staff will monitor you and know how to treat a seizure should one occur.

The effects of rTMS 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 urinal pregnancy test prior to commencing rTMS. This test will be processed by a female member of the research staff.

If you do become pregnant whilst participating in the research project, you should advise research staff immediately. The researchers 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 rTMS.

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

Magnetic Resonance Imaging (MRI)

MRI stands for magnetic resonance imaging. An MRI scanner is a machine that uses electromagnetic radiation (radio waves) in a strong magnetic field to take clear pictures of the inside of the body. Electromagnetic radiation is not the same as ionising radiation used, for example, in X-rays. The pictures taken by the machine are called MRI scans.

There are no proven long-term risks related to MRI scans as used in this research project. MRI is considered to be safe when performed at a centre with appropriate procedures. However, the magnetic attraction for some metal objects can pose a safety risk, so it is important that metal objects are not taken into the scanner room.

We will thoroughly examine you to make sure there is no reason for you not to have the scan. You must tell us if you have metal implanted in your body, such as a pacemaker or metal pins.

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 become uncomfortable during the session, we can pause or stop the scanning.

The scans we are taking are for research purposes. They are not intended to be used like scans taken for a full clinical examination. The scans will not be used to help diagnose, treat, or manage a particular condition. A specialist will look at your MRI scans for features relevant to the research project. On rare occasions, the specialist may find an unusual feature that could have a significant risk to your health. If this happens, we will contact you to talk about the findings. We cannot guarantee that we will find any/all unusual features. 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.

If you become upset or distressed as a result of your participation in the research, the study doctor will be able to arrange for counselling or other appropriate support. Any counselling or support will be provided by qualified staff who are not members of the research project team. This counselling will be provided free of charge.

9 What will happen to my test samples?

You will be asked to provide additional consent for the collection of your tissue (i.e., cheek swab) during the research project. As noted, these samples are collected to allow us to investigate whether certain genetic profiles are associated with a better response to the rTMS intervention. We will only conduct these analyses at a group level. You will not receive any health information (e.g., genetic disease predisposition) from these genetic analyses, and they are not considered to be clinically informative. Your genetic material and information, where

identified or potentially identifiable, will not be released for other uses without your prior consent, unless required by law.

Samples of your tissue obtained for the purpose of this research project will be transferred to the Institute for Molecular Bioscience, University of Queensland, who will charge a fee to the research team to recover some of the costs of storing and administering the tissue samples. The University of Queensland will not transfer or sell your samples to any third party.

10 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, your study doctor might consider it to be in your best interests to withdraw you from the research project. If this happens, your study doctor will explain the reasons and arrange for your regular health care to continue.

11 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 research 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.

Because this trial is assessing the effect of rTMS on social communication, you cannot participate if you are also undergoing any other treatment or intervention for social communication. This includes interventions delivered by psychologists.

12 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 doctor and relevant 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 up to the time you withdraw will form part of the research project results. If you do not want the researchers to do this, you must tell them before you join the research project.

13 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 drug/treatment/device being shown not to be effective
- The drug/treatment/device being shown to work and not need further testing
- Decisions made by local regulatory/health authorities.

14 What happens when the research project ends?

You will be sent a summary of the main findings when the project has been completed. This is a 4-year study and it is expected that study results will be available by late 2024. Your data will then be securely archived at Deakin University.

Please note that rTMS will not be available from the research sites after completing the study. It may be approved for future use in ASD, but this will depend on the results from the current study.

Part 2 How is the research project being conducted?

15 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. Upon enrolment in the trial you will be allocated a unique study identification code. Your name will not appear with the research data that we collect from you and it will only be possible to re-identify your data using the study code. Only the research team will know which code identifies which participant. Your information will only be used for the purpose of this research project and future research projects, and it will only be disclosed with your permission, except as required by law.

Information about you may be obtained from your health records held at this and other health services for the purpose of this research. By signing the consent form, you agree to the study team accessing health records if they are relevant to your participation in this research project.

Your health records and any information obtained during the research project are subject to inspection (for the purpose of verifying the procedures and the data) by the relevant authorities and authorised representatives of the Sponsor, Deakin University, the institution relevant to this Participant Information Sheet, *[Name of institution]*, or as required by law. By signing the Consent Form, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

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. We will only present group-level findings (e.g., average scores across the group) and no individual data will be reported.

In accordance with relevant Australian *and/or [Name of state/territory]* 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 and for future research 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.

It is expected that deidentified data from this study will be made available to other researchers via online data repositories. You will not be able to be identified in these repositories. It is also possible that the research team will use your data from this research project for future studies, but again you will not be able to be identified.

16 Complaints and compensation

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.

If you have complaints about your treatment by members of staff working on this research project, you should contact the person nominated in Section 19 below. If you have complaints about any of the ethical aspects of this study, you can contact the local reviewing HREC Executive Officer nominated in Section 19 below. Complaints about clinical trials can also be directed to the Office of the Australian Information Commissioner.

17 Who is organising and funding the research?

This research project is being conducted by a team of researchers led by Prof. Peter Enticott from Deakin University, Victoria. It is funded through a Medical Research Future Fund grant from the National Health and Medical Research Council to Prof. Enticott and the research team.

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

18 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 HREC of Monash Health and *[Name of institutions]*.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2018)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

19 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 that may be related to your involvement in the project (for example, any side effects), you can contact your site's principal study doctor on *[phone number]* or any of the following people:

Study contact person

Name	*[Name]*
Position	*[Position]*
Telephone	*[Phone number]*
Email	*[Email address]*

Clinical contact person

Name	*[Name]*
Position	*[Position]*
Telephone	*[Phone number]*
Email	*[Email address]*

For matters relating to research at the site at which you are participating, the details of the local site complaints person are:

Complaints contact person

Name	*[Name]*
Position	*[Position]*
Telephone	*[Phone number]*
Email	*[Email address]*

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 approving this research and HREC Executive Officer details

Reviewing HREC name	*Monash Health*
HREC Executive Officer	*Ms Deborah Dell*
Telephone	*(03) 9594 4605*
Email	*research@monashhealth.org*

Local HREC Office contact (Single Site - Research Governance Officer)

Name	*[Name]*
Position	*[Position]*
Telephone	*[Phone number]*
Email	*[Email address]*

Consent Form - *Adult providing own consent*

Title	*Does repetitive transcranial magnetic stimulation (rTMS), compared to sham rTMS, improve social communication in adolescents and young adults with autism spectrum disorder (ASD)?*
Short Title	*MRFF RTMS-ASD*
Protocol Number	*v2, 11/09/2020*
Project Sponsor	*Deakin University*
Coordinating Principal Investigator	*Prof. Peter Enticott*
Associate Investigator(s)	*Prof. Paul Fitzgerald, A/Prof. Karen Barlow, Prof. Ian Hickie, Dr Melissa Licari, Dr Nigel Rogasch, Prof. Christel Middeldorp, Dr Scott Clark, Dr Ann-Maree Vallence, Dr Kelsie Boulton, Prof. Adam Guastella, Prof. Andrew Whitehouse, Prof. Cherrie Galletly, Dr Gail Alvares, Dr Hakuei Fujiyama, A/Prof. Helen Heussler, A/Prof. Jeffrey Craig, Dr Melissa Kirkovski, Dr Natalie Mills, Prof. Nicole Rinehart, Dr Peter Donaldson, Dr Talitha Ford, Prof. Karen Caeyenberghs*
Location	*[Location where the research will be conducted]*

Consent Agreement

I have read the Participant Information Sheet.

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 *[Name of Institution]* concerning my condition 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 agree for my anonymous study data to be shared with other researchers, including those outside *[Name of Institution]* and outside Australia, for future studies.

I agree to my anonymised data being made available through online repositories and to the use of my data in any future research.

Declaration by Participant – for participants who have read the information

Name of Participant (please print) _____

Signature _____ Date _____

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.

I consent to the storage and use of tissue samples (cheek swabs) taken from me for use, as described in the relevant section of the Participant Information Sheet, for:

- This specific research project
- Other research that is closely related to this research project
- Any future research.

By signing this consent section, I agree to the use of my tissue samples for genetic testing, as outlined in the relevant Section of the Participant Information Sheet.

Name of Participant (please print) _____

Signature _____ Date _____

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	*Does repetitive transcranial magnetic stimulation (rTMS), compared to sham rTMS, improve social communication in adolescents and young adults with autism spectrum disorder (ASD)?*
Short Title	*MRFF RTMS-ASD*
Protocol Number	*v2, 11/09/2020*
Project Sponsor	*Deakin University*
Coordinating Principal Investigator	*Prof. Peter Enticott*
Associate Investigator(s)	*Prof. Paul Fitzgerald, A/Prof. Karen Barlow, Prof. Ian Hickie, Dr Melissa Licari, Dr Nigel Rogasch, Prof. Christel Middeldorp, Dr Scott Clark, Dr Ann-Maree Vallence, Dr Kelsie Boulton, Prof. Adam Guastella, Prof. Andrew Whitehouse, Prof. Cherrie Galletly, Dr Gail Alvares, Dr Hakuei Fujiyama, A/Prof. Helen Heussler, A/Prof. Jeffrey Craig, Dr Melissa Kirkovski, Dr Natalie Mills, Prof. Nicole Rinehart, Dr Peter Donaldson, Dr Talitha Ford, Prof. Karen Caeyenberghs*
Location	*[Location where the research will be conducted]*

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 *[Institution]*.

Name of Participant (please print) _____

Signature _____ Date _____

Description of circumstances where communicated verbally:

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.

Insert Header with institution's name or institution's letterhead

Participant Information Sheet/Consent Form

Interventional Study - *Parent/Guardian consenting on behalf of participant*

[Insert site name]

Title	*Does repetitive transcranial magnetic stimulation (rTMS), compared to sham rTMS, improve social communication in adolescents and young adults with autism spectrum disorder (ASD)?*
Short Title	*MRFF TBS-ASD*
Protocol Number	*v2, 11/09/2020*
Project Sponsor	*Deakin University*
Coordinating Principal Investigator	*Prof. Peter Enticott*
Associate Investigator(s)	*Prof. Paul Fitzgerald, A/Prof. Karen Barlow, Prof. Ian Hickie, Dr Melissa Licari, Dr Nigel Rogasch, Prof. Christel Middeldorp, Dr Scott Clark, Dr Ann-Maree Vallence, Dr Kelsie Boulton, Prof. Adam Guastella, Prof. Andrew Whitehouse, Prof. Cherrie Galletly, Dr Gail Alvares, Dr Hakuei Fujiyama, A/Prof. Helen Heussler, A/Prof. Jeffrey Craig, Dr Melissa Kirkovski, Dr Natalie Mills, Prof. Nicole Rinehart, Dr Peter Donaldson, Dr Talitha Ford, Prof. Karen Caeyenberghs*
Location	*[Insert site-specific location]*

Part 1 What does the child's participation involve?

1 Introduction

This is an invitation for the child in your care to take part in this research project because they have been diagnosed with autism spectrum disorder (ASD). The research project is testing a new treatment for ASD. The new treatment is called 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 your child 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 your child can take part, you might want to talk about it with a relative, friend or your child's local doctor.

Participation in this research is voluntary. If you do not wish your child to take part, they do not have to. Your child will receive the best possible care whether or not they take part.

If you decide you want your child 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 your child taking part in the research project
- Consent for your child to have the tests and treatments that are described
- Consent to the use of your child's 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 and 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 rTMS can be used to improve social function. rTMS is a safe and non-invasive means of stimulating nerve cells in a particular part of the brain via the administration of brief magnetic pulses. rTMS has been developed as a treatment for major depressive disorder, and we have previously found that rTMS can benefit social aspects of ASD.

In this study we will stimulate a region of the brain that is involved in social understanding and social communication. This region is called the right temporoparietal junction, or rTPJ.

Some participants will receive the real form of rTMS, while others will receive a sham or placebo form. The sham or placebo form mimics the feeling of rTMS, but no brain stimulation is delivered. You will not know which one your child receives until the end of your involvement in the study. Those who received the sham or placebo form will be given the opportunity to undergo the real rTMS treatment at the end of their involvement in the study.

150 people (aged 14-40 years) will take part in this study, which is being conducted throughout Australia. There are sites in Brisbane, Sydney, Melbourne, Adelaide, and Perth. Participants will be recruited from around Australia, but primarily the greater metropolitan regions within these five cities.

rTMS 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, Prof. Peter Enticott (Deakin University, Melbourne). This research has been funded by the National Health and Medical Research Council (NHMRC) of Australian through a Medical Research Future Fund grant (MRFF RCRDUN Neurological Disorders 2020; Application APP1199298).

3 What does participation in this research involve?

Your child will be participating in a randomised controlled research project. Sometimes we do not know which treatment is best for treating a condition. To find out we need to compare different treatments. We put people into groups and give each group a different treatment (in this case, real RTMS vs. sham/placebo RTMS). The results are compared to see if one is better. To try to make sure the groups are the same, each participant is put into a group by chance (random).

This is a double-blind study. This means that it will not be known which of the treatments your child is receiving (in this case, real rTMS or sham/placebo rTMS); the study doctor will also not know. However, in certain circumstances your study doctor can find out which treatment your child is receiving. Participants will be randomly allocated to either the real rTMS or sham/placebo RTMS condition. As mentioned, those allocated to the sham or placebo form will be given the opportunity to undergo the real rTMS treatment at the end of their involvement in the study.

This research project has been designed to make sure the researchers interpret the results in a fair and appropriate way and avoids study doctors or participants jumping to conclusions.

If you decide that your child can participate in this research project, you and your child will be asked to take part in a number of interviews and procedures over the course of approximately eight months. These are outlined below. You (or another parent/guardian of the child) must attend each session with your child.

Prior to completing the study, we will need to determine your child's eligibility to take part in the study. We will do this by asking you questions (either over the phone or via email) about their health. We will also ask you to provide a letter or report confirming your child's diagnosis of ASD; if you are not able to provide this, we will seek permission (via the consent form) to contact your child's doctor or psychologist directly to confirm their diagnosis.

Assessment Session One: The first assessment will take place at [site-specific location]. It will take approximately three hours, but your child will be given regular breaks throughout the session.

We will begin by asking you some questions about your child's health, which will help to confirm their eligibility to take part in the study. We will then ask you some questions about your child that are relevant to ASD. This will include, for example, what they enjoy doing and how much they like being with other people.

Your child will complete a short cognitive assessment, which involves solving puzzles and describing what different words mean.

Finally, your child will undergo electroencephalography (EEG), which involves wearing an "electrode cap" to measure the electrical activity of their brain, or their "brainwaves." The electrode cap feels similar to a swimming cap. It will also feel a little damp, as we need to put a small amount of gel or saline into the cap to ensure that we get accurate recordings. For most of the EEG your child will simply rest while sitting in a chair, but your child will also complete a short task on a computer that involves looking at different objects (e.g., faces, household furniture, butterflies).

Assessment Session Two: Around one-week after "Assessment Session One" your child will then undergo a magnetic resonance imaging (MRI) brain scan at [site-specific location]. The MRI brain scan takes around 45-60 minutes, during which they will be asked to lie still in an MRI scanner. (Please note that with preparation time you attend the MRI facility for up to two hours.) MRI is a routinely performed, painless ways of examining brain structure and activity. We will use the MRI to accurately place the rTMS device and ensure that we are stimulating the correct brain region. The MRI procedure may also help us better understand how the treatment works and to determine who is likely to respond to treatment and why.

Assessment Session Three: During the same week of "Assessment Session Two," you and your child will attend a two-hour assessment session at [site-specific location]. Here we will ask you questions about your child, some of which are relevant to ASD, while others relate to their concentration and behaviour. Your child will also be asked some questions about their mood, stress, and satisfaction with life. We will also ask your child to complete some cognitive tasks on a computer/tablet. These tasks measure their memory, attention, and understanding of other people's emotions. We will also ask your child to provide a sample for genetic analysis; this will involve them having a cotton swab rubbed against the inside of their cheek. These genetic analyses are conducted to investigate whether people with certain genetic profiles respond better to the intervention. You will not receive any health information from these genetic analyses, and they are not considered to be clinically informative.

rTMS Intervention (4 weeks): The week after "Assessment Session Three" your child will begin the rTMS intervention, which involves attending [site-specific location] and receiving rTMS

for 3 minutes, 20 seconds each consecutive weekday for a four-week period (20 RTMS sessions in total).

Your child will have their first rTMS session on the Monday after “Assessment Session Three.” At the beginning of the first session we will administer transcranial magnetic stimulation (TMS) to the area of the brain that controls the muscles in their hand. This will measure how excitable their brain is and is used to help us determine the personalised settings that will be used for their rTMS treatments. This takes approximately 10 minutes and is not uncomfortable, although they may feel some twitches in the muscle of their hand while the TMS is occurring.

During each rTMS session your child will be awake, alert, and aware of what is happening at all times. During rTMS a coil will be placed against their head, through which rTMS 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 sensations associated with rTMS are mild, and most people describe it as a “tapping” sensation on their head. During an rTMS procedure, your child will hear clicking sounds as the current passes through the coil. Your child will wear earplugs so that this noise doesn’t disturb them.

Including setup time, each subsequent treatment session should only take approximately 10 minutes. At the end of each treatment week (i.e., on the Friday session) we will ask you and your child a number of questions about their experience of RTMS, and whether you feel that they have experienced any side effects.

Assessment Session Four: The week after your child’s last RTMS session, you and your child will attend another two-hour assessment session at [site-specific location]. Here we will again ask you questions about your child, some of which are relevant to ASD, while others relate to their concentration and behaviour. Your child will also be asked some questions about their mood, stress, and satisfaction with life. We will also again ask your child to complete some cognitive tasks on a computer/tablet and to provide another sample (cheek swab) for genetic analysis.

Assessment Session Five: One-month after your child’s last RTMS session, you and your child will attend another two-hour assessment session at [site-specific location]. This session will be identical to Assessment Session Four.

Assessment Session Six: Three-months after your child’s last RTMS session, you and your child will attend a one-hour assessment session at [site-specific location]. This session will be identical to Assessment Session Five except that your child will not complete the computerised cognitive tasks.

Assessment Session Seven: Six-months after your child’s last RTMS session, you and your child will attend a final two-hour assessment session at [site-specific location]. This session will be identical to Assessment Session Four. Following the assessment you will be unblinded; that is, a member of the research team will tell you and your child which treatment condition your child received (i.e., real or sham/placebo). If your child received the real treatment, you and your child’s involvement in the study will conclude. If your child received the sham/placebo condition, your child will be given the opportunity to receive the real treatment. You can liaise with research staff to determine when you would like your child to undergo this four-week treatment.

There are no costs associated with participating in this research project. All treatments, tests, and medical care required as part of the research project will be provided to your child free of charge.

You will not be paid for you and your child’s participation in this research, but you will be reimbursed $200 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 decide 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.

It is desirable that your child's local doctor be advised of your decision for your child to participate in this research project. If you have a local doctor, we strongly recommend that you inform them of your child's participation in this research project.

The research will be monitored by an independent Data Safety Monitoring Board, who will meet twice per year and review the conduct of the trial, monitor study data, and review any serious adverse events that might arise throughout the trial.

4 What does the child have to do?

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

There are several reasons why your child 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, or evidence of significant seizure activity as assessed by EEG
- 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)
- Being deemed unsuitable to undergo MRI (e.g., due to presence of metal in the body)
- Unstable medical condition
- Unstable medication regime
- Certain medications
- Substance use disorder
- Undergoing another current treatment for social communication
- Employment as a professional driver or machine operator (as the event of a seizure may affect employment)
- Pregnancy (female participants for whom child-bearing is a possibility will be required to undergo a urine screen)
- Certain neurological or psychiatric diagnoses (i.e., those not commonly associated with ASD, such as psychosis)
- A measured verbal intelligence quotient (IQ) of less than 55

5 Other relevant information about the research project

This study is only taking place in Australia. There will be 150 participants in this study, with 30 taking part in each of the five cities involved: Brisbane, Sydney, Melbourne, Adelaide, and Perth. There are a total of 14 organisations involved, including Universities, hospitals, and medical centres. This study is a follow-on study from our previous trials of rTMS in ASD, which have taken place at Monash University, Deakin University, The Alfred hospital, and the Epworth Camberwell.

6 Does the child have to take part in this research project?

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

If you do decide that the child can take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep. If your child has the capacity to provide informed consent, they may also sign the consent form.

Your decision that the child can or cannot take part, or that they can take part and then be withdrawn, will not affect their routine treatment, relationship with those treating them, or their relationship with *[site-specific Institution/s]*.

7 What are the possible benefits of taking part?

We cannot guarantee or promise that your child will receive any benefits from this research; however, possible benefits 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?

Repetitive Transcranial Magnetic Stimulation (rTMS)

Medical treatments often cause side effects. Your child may have none, some, or all of the effects listed below, and they may be mild, moderate, or severe. If your child has any of these side effects, or you are worried about them, talk with your study doctor. Your child's 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 your child gets.

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 child's treatment. The child's study doctor will discuss the best way of managing any side effects with you.

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

Headache: A headache can occur during rTMS and is thought to affect approximately 3% or 3 in 100 participants. It is thought to be caused by stimulation of nerves in the scalp. If your child were to experience such a headache, it will respond quickly to simple pain medication such as aspirin, ibuprofen, or paracetamol.

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

Seizure: The main concern associated with rTMS 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 such individuals). If your child has ever experienced a seizure, or if their EEG shows evidence of epileptiform activity, they will not be able to take part in this study. Investigators using rTMS have developed safety guidelines to minimise the risk of seizure. The RTMS 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 your child has rTMS. Staff will monitor your child and know how to treat a seizure should one occur.

The effects of rTMS 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. Individuals must not participate in the research if they are pregnant or trying to become pregnant, or breast-feeding. If your child is female and child-bearing is a possibility, they will be required to undergo a urinal pregnancy test prior to commencing rTMS. This test will be processed by a female member of the research staff.

If a participant becomes pregnant whilst participating in the research project, they should advise research staff immediately. The researchers will withdraw them from the research project and advise on further medical attention should this be necessary. An individual must not continue in the research if they become pregnant.

The ability to drive or use public transport will not be impaired following rTMS.

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

Magnetic Resonance Imaging (MRI)

MRI stands for magnetic resonance imaging. An MRI scanner is a machine that uses electromagnetic radiation (radio waves) in a strong magnetic field to take clear pictures of the inside of the body. Electromagnetic radiation is not the same as ionising radiation used, for example, in X-rays. The pictures taken by the machine are called MRI scans.

There are no proven long-term risks related to MRI scans as used in this research project. MRI is considered to be safe when performed at a centre with appropriate procedures. However, the magnetic attraction for some metal objects can pose a safety risk, so it is important that metal objects are not taken into the scanner room.

We will thoroughly examine your child to make sure there is no reason for them not to have the scan. You must tell us if your child has metal implanted in their body, such as a pacemaker or metal pins.

The MRI scanner is shaped like a narrow tunnel. Foam cushioning and Velcro straps are used to keep your child's 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 your child has experienced claustrophobia in the past. The MRI scanner is noisy, so your child will wear ear plugs and headphones to reduce the noise. We will be able to see your child and communicate with them during the scanning, and they will be able to stop the machine at any time by pushing a button. If they become uncomfortable during the session, we can pause or stop the scanning.

The scans we are taking are for research purposes. They are not intended to be used like scans taken for a full clinical examination. The scans will not be used to help diagnose, treat, or manage a particular condition. A specialist will look at your child's MRI scans for features relevant to the research project. On rare occasions, the specialist may find an unusual feature that could have a significant risk to your child's health. If this happens, we will contact you to talk about the findings. We cannot guarantee that we will find any/all unusual features. There may be wider implications from abnormal findings (e.g., for future applications for some kinds of insurance).

Other

We will ask you and your child if they 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 them in legal proceedings or otherwise.

If you or your child become upset or distressed as a result of your participation in the research, the study doctor will be able to arrange for counselling or other appropriate support. Any counselling or support will be provided by qualified staff who are not members of the research project team. This counselling will be provided free of charge.

9 What will happen to the child's test samples?

You will be asked to provide additional consent for the collection of your child's tissue (i.e., cheek swab) during the research project. As noted, these samples are collected to allow us to investigate whether certain genetic profiles are associated with a better response to the rTMS intervention. We will only conduct these analyses at a group level. You will not receive any health information (e.g., genetic disease predisposition) from these genetic analyses, and they are not considered to be clinically informative. Your child's genetic material and information, where identified or potentially identifiable, will not be released for other uses without your prior consent, unless required by law.

Samples of your child's tissue obtained for the purpose of this research project will be transferred to the Institute for Molecular Bioscience, University of Queensland, who will charge a fee to the research team to recover some of the costs of storing and administering the tissue samples. The University of Queensland will not transfer or sell your child's samples to any third party.

10 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 child's study doctor will tell you about it and discuss with you whether you want your child to continue in the research project. If you decide to withdraw your child from the study, your child's study doctor will make arrangements for their regular health care to continue. If you decide to continue your child's involvement in the research project you will be asked to sign an updated consent form.

Also, on receiving new information, your child's study doctor might consider it to be in your child's best interests to withdraw them from the research project. If this happens, your child's study doctor will explain the reasons and arrange for your regular health care to continue.

11 Can the child have other treatments during this research project?

Whilst your child is participating in this research project, they can continue to take the medications or treatments they have been taking for their condition or for other reasons. It is important to tell the research staff about any treatments or medications your child is 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 child's participation in the research project.

Because this trial is assessing the effect of rTMS on social communication, your child cannot participate if they are also undergoing any other treatment or intervention for social communication. This includes interventions delivered by psychologists.

12 What if I withdraw the child from this research project?

If you decide to withdraw your child 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 for your child's participation during the research project, the study doctor and relevant study staff will not collect additional personal information from you or your child, 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 up to the time you withdraw your child will form part of the research project results. If you do not want them to do this, you must tell the researchers before your child joins the research project.

13 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 drug/treatment/device being shown not to be effective
- The drug/treatment/device being shown to work and not need further testing
- Decisions made by local regulatory/health authorities.

14 What happens when the research project ends?

You will be sent a summary of the main findings when the project has been completed. This is a 4-year study and it is expected that study results will be available by late 2024. Your child's data will then be securely archived at Deakin University.

Please note that RTMS will not be available from the research sites after completing the study. It may be approved for future use in ASD, but this will depend on the results from the current study.

Part 2 How is the research project being conducted?

15 What will happen to information about my child?

By signing the consent form, you consent to the study doctor and relevant research staff collecting and using personal information about your child for the research project. Any information obtained in connection with this research project that can identify your child will remain confidential. Upon enrolment in the trial your child will be allocated a unique study identification code. Your child's name will not appear with the research data that we collect from you and them, and it will only be possible to re-identify your child's data using the study code. Only the research team will know which code identifies which participant. Your child's information will only be used for the purpose of this research project and future research projects, and it will only be disclosed with your permission, except as required by law.

Information about your child may be obtained from your child's health records held at this and other health services for the purpose of this research. By signing the consent form, you agree to the study team accessing your child's health records if they are relevant to your child's participation in this research project.

Your child's health records and any information obtained during the research project are subject to inspection (for the purpose of verifying the procedures and the data) by the relevant authorities and authorised representatives of the Sponsor, Deakin University, the institution relevant to this Participant Information Sheet, *[Name of institution]*, or as required by law. By signing the Consent Form, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

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 your child cannot be identified, except with your permission. We will only present

group-level findings (e.g., average scores across the group) and no individual data will be reported.

In accordance with relevant Australian *and/or [Name of state/territory]* privacy and other relevant laws, you have the right to request access to your child's 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 child's information.

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

It is expected that deidentified data from this study will be made available to other researchers via online data repositories. Your child will not be able to be identified in these repositories. It is also possible that the research team will use your child's data from this research project for future studies, but again they will not be able to be identified.

16 Complaints and compensation

If your child 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.

If you have complaints about you or your child's treatment by members of staff working on this research project, you should contact the person nominated in Section 19 below. If you have complaints about any of the ethical aspects of this study, you can contact the local reviewing HREC Executive Officer nominated in Section 19 below. Complaints about clinical trials can also be directed to the Office of the Australian Information Commissioner.

17 Who is organising and funding the research?

This research project is being conducted by a team of researchers led by Prof. Peter Enticott from Deakin University, Victoria. It is funded through a Medical Research Future Fund grant from the National Health and Medical Research Council to Prof. Enticott and the research team.

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

18 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 HREC of Monash Health and *[Name of institutions]*.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2018)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

19 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 your child has any medical problems that may be related to their involvement in the project (for example, any side effects),

you can contact your site's principal study doctor on *[phone number]* or any of the following people:

Study contact person

Name	*[Name]*
Position	*[Position]*
Telephone	*[Phone number]*
Email	*[Email address]*

Clinical contact person

Name	*[Name]*
Position	*[Position]*
Telephone	*[Phone number]*
Email	*[Email address]*

For matters relating to research at the site at which you are participating, the details of the local site complaints person are:

Complaints contact person

Name	*[Name]*
Position	*[Position]*
Telephone	*[Phone number]*
Email	*[Email address]*

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 approving this research and HREC Executive Officer details

Reviewing HREC name	*Monash Health*
HREC Executive Officer	*Ms Deborah Dell*
Telephone	*(03) 9594 4605*
Email	*research@monashhealth.org*

Local HREC Office contact (Single Site - Research Governance Officer)

Name	*[Name]*
Position	*[Position]*
Telephone	*[Phone number]*
Email	*[Email address]*

Consent Form - *Adult providing own consent*

Title	*Does repetitive transcranial magnetic stimulation (rTMS), compared to sham rTMS, improve social communication in adolescents and young adults with autism spectrum disorder (ASD)?*
Short Title	*MRFF RTMS-ASD*
Protocol Number	*v2, 11/09/2020*
Project Sponsor	*Deakin University*
Coordinating Principal Investigator	*Prof. Peter Enticott*
Associate Investigator(s)	*Prof. Paul Fitzgerald, A/Prof. Karen Barlow, Prof. Ian Hickie, Dr Melissa Licari, Dr Nigel Rogasch, Prof. Christel Middeldorp, Dr Scott Clark, Dr Ann-Maree Vallence, Dr Kelsie Boulton, Prof. Adam Guastella, Prof. Andrew Whitehouse, Prof. Cherrie Galletly, Dr Gail Alvares, Dr Hakuei Fujiyama, A/Prof. Helen Heussler, A/Prof. Jeffrey Craig, Dr Melissa Kirkovski, Dr Natalie Mills, Prof. Nicole Rinehart, Dr Peter Donaldson, Dr Talitha Ford, Prof. Karen Caeyenberghs*
Location	*[Location where the research will be conducted]*

Consent Agreement

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 the child's doctors, other health professionals, hospitals or laboratories outside this hospital to release information to *[Name of Institution]* concerning the child's 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 the child participating in this research project as described and understand that I am free to withdraw them at any time during the research project without affecting their future health care.

I freely agree to participate in this research project as described (e.g., completion of questionnaires) 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 agree for my child's anonymous study data to be shared with other researchers, including those outside *[Name of Institution]* and outside Australia, for future studies.

I agree to my child's anonymised data being made available through online repositories and to the use of my data in any future research.

Declaration by Parent/Guardian – for Parent/Guardian who has read the information

Name of Child (please print) _____

Name of Parent/Guardian (please print) _____

Signature of Parent/Guardian _____ Date_____

Declaration by Young Person – for participants under the age of 18 who have capacity to provide informed consent

Name of Young Person (please print) _____

Signature of Young Person _____ Date_____

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.

Continued on next page

I consent to the storage and use of tissue samples (cheek swabs) taken from my child for use, as described in the relevant section of the Participant Information Sheet, for:

- This specific research project
- Other research that is closely related to this research project
- Any future research.

By signing this consent section, I agree to the use of my child's tissue samples for genetic testing, as outlined in the relevant Section of the Participant Information Sheet.

Name of Child (please print) _____

Name of Parent/Guardian (please print) _____

Signature of Parent/Guardian _____ Date _____

Name of Young Person (please print) _____

Signature of Young Person _____ Date _____

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 - *Parent/Guardian consenting on behalf of participant*

Title	*Does repetitive transcranial magnetic stimulation (rTMS), compared to sham rTMS, improve social communication in adolescents and young adults with autism spectrum disorder (ASD)?*
Short Title	*MRFF RTMS-ASD*
Protocol Number	*v2, 11/09/2020*
Project Sponsor	*Deakin University*
Coordinating Principal Investigator	*Prof. Peter Enticott*
Associate Investigator(s)	*Prof. Paul Fitzgerald, A/Prof. Karen Barlow, Prof. Ian Hickie, Dr Melissa Licari, Dr Nigel Rogasch, Prof. Christel Middeldorp, Dr Scott Clark, Dr Ann-Maree Vallence, Dr Kelsie Boulton, Prof. Adam Guastella, Prof. Andrew Whitehouse, Prof. Cherrie Galletly, Dr Gail Alvares, Dr Hakuei Fujiyama, A/Prof. Helen Heussler, A/Prof. Jeffrey Craig, Dr Melissa Kirkovski, Dr Natalie Mills, Prof. Nicole Rinehart, Dr Peter Donaldson, Dr Talitha Ford, Prof. Karen Caeyenberghs*
Location *(where CPI/PI will recruit)*	*[Location where the research will be conducted]*

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 *[Institution]*.

Name of Child (please print) _____

Name of Parent/Guardian (please print) _____

Signature of Parent/Guardian _____ Date_____

Name of Young Person (please print) _____

Signature of Young Person _____ Date_____

Description of circumstances where communicated verbally:

Continued on next page

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.

BIOLOGICAL SPECIMENS

Participants will be administered a buccal swab on two occasions, which involves rubbing a cotton bud against the inside of the cheek. These will be collected in person by a member of the research team at each site. Specimens will then be sealed in a DNA/RNA Shield tube and labelled with the participant's unique study identification code. It will then be transported by courier/post to the Institute of Molecular Bioscience, University of Queensland, for extraction, storage, and analysis.

Numerical data arising from genetic and epigenetic analyses will be sent electronically to the research team (Chief Investigators Prof. Enticott and Prof. Middeldorp) and stored in REDCap databases. PDF files containing results will also be stored in REDCap.

The research team will retain all biospecimens, which will be securely stored at the Institute of Molecular Bioscience, University of Queensland. This will allow the possibility of future analyses, particularly to determine genetic and epigenetic factors associated with a clinical response to the TBS intervention. The research team may contribute results from these data to future collaborative projects, which may involve external researchers who are not involved in the current trial. No information that could identify a participant will be shared. Participants (and their parent/guardian where necessary) will be asked to provide permission for future biospecimen use as part of the informed consent procedure.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page Number on which item is reported
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	15
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	7, 13
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	7
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6-10
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	n/a
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	n/a
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8-9

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 1, 11-12
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8-9
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9-10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9-10
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	13
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	9

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	13
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Appendix
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	13
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13-14

	31b	Authorship eligibility guidelines and any intended use of professional writers	13
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	10, 14
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Appendix

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.