Ethics Study Protocol

M	
Full study title	CLIBM: Closed-loop non-invasive stimulation for improving brain and mental health in healthy individuals
Short title	Closed-loop tES-non-invasive stimulation
Ethics REC reference	F1781
Date and version number	20/10/2026 Version 3
Principal investigator	Professor Marcus Kaiser
University email contact	marcus.kaiser@nottingham.ac.uk
Student (if applicable)	
University email contact	
University telephone contact	
Medically qualified collaborator (licensed doctor)	
Sponsor	The University of Nottingham
External funding	
Declaration of any conflicts of interest	None
Confidentiality statement	This document contains confidential information that must not be disclosed to anyone other than the authorised individuals from the University of Nottingham, the Investigator Team and members of the Faculty of Medicine & Health Sciences University Research Ethics Committee (FMHS REC), unless authorised to do so.

RESEARCH TEAM	
Principal investigator (PI) title and name, qualifications, job title	Professor Marcus Kaiser, Ph.D. FRSB, Professor of Neuroinformatics
Department/institute name	Precision Imaging Beacon, Mental Health and Clinical Neurosciences, School of Medicine
Role in study	To provide oversight of the project and hold responsibility for delivery.
Training/qualification in research ethics	Research ethics training appropriate to grade completed, GCP up to date.
Research Integrity Training	Research Integrity courses have been completed
UoN Code of Research Conduct and Research Ethics	Yes
Title and name, qualifications, job title	Professor Stephen Jackson, Ph.D, Professor of Cognitive Neuroscience
Department/institute name	Mental Health and Clinical Neurosciences, Institute of mental Health, School of Medicine
Role in study	Co - investigators
Training/qualification in research ethics	Research ethics training appropriate to grade completed, GCP up to date.
Research Integrity Training	Research Integrity courses have been completed
UoN Code of Research Conduct and Research Ethics	Yes
title and name, qualifications, job title	Professor Dorothee Auer, Professor of Neuroimaging
Department/institute name	Precision Imaging Beacon, Mental Health and Clinical Neurosciences, School of Medicine
Role in study	Co - investigators
Training/qualification in research ethics	Research ethics training appropriate to grade completed
Research Integrity Training	Research Integrity courses have been completed
UoN Code of Research Conduct and Research Ethics	Yes
title and name, qualifications, job title	Professor Stam Sotiropoulos, Ph.D, Professor of Computational Neuroimaging
Department/institute name	Precision Imaging Beacon, Mental Health and Clinical Neurosciences, School of Medicine
Role in study	Co - investigators

Training/qualification in research ethics	Research ethics training appropriate to grade completed
Research Integrity Training	Research Integrity courses have been completed
UoN Code of Research Conduct and Research Ethics	Yes
title and name, qualifications, job title	Professor Mohammad Zia Ul Haq Katshu, Clinical Associate Professor
Department/institute name	Mental Health and Clinical Neurosciences, Institute of mental Health, School of Medicine
Role in study	Co - investigators
Training/qualification in research ethics	Research ethics training appropriate to grade completed
Research Integrity Training	Research Integrity courses have been completed
UoN Code of Research Conduct and Research Ethics	Yes
UoN Code of Research Conduct and Research Ethics	Yes
title and name, qualifications, job title	Paul Briley, Clinical Assistant professor in general adult psychiatry
Department/institute name	Mental Health and Clinical Neurosciences, School of Medicine
Role in study	Co - investigator
Training/qualification in research ethics	Research ethics training appropriate to grade completed
Research Integrity Training	Research Integrity courses have been completed
UoN Code of Research Conduct and Research Ethics	Yes
title and name, qualifications, job title	Dr Jeyoung Jung, Assistant Professor
Department/institute name	School of Psychology Precision Imaging/Centre for Dementia
Role in study	Co - investigators
Training/qualification in research ethics	Research ethics training appropriate to grade completed
Research Integrity Training	Research Integrity courses have been completed
UoN Code of Research Conduct and Research Ethics	Yes
title and name, qualifications, job title	Dr. Alicia Falcon Caro, Ph.D, Postdoctoral Research Fellow
Department/institute name	Precision Imaging Beacon, Mental Health and Clinical Neurosciences, School of Medicine
Role in study	Co-investigator
Training/qualification in research ethics	Research ethics training appropriate to grade completed, GCP completed
Research Integrity Training	Research Integrity courses have been completed

UoN Code of Research Conduct and Research Ethics	Yes
title and name, qualifications, job title	Dr. Daniel Halls, Ph.D, Postdoctoral Research Fellow
Department/institute name	Precision Imaging Beacon, Mental Health and Clinical Neurosciences, School of Medicine
Role in study	Co - investigators
Training/qualification in research ethics	Research ethics training appropriate to grade completed
Research Integrity Training	Research Integrity courses have been completed
UoN Code of Research Conduct and Research Ethics	Yes
title and name, qualifications, job title	Stefanos Kontogouris, Ph.D student
Department/institute name	Precision Imaging Beacon, Mental Health and Clinical Neurosciences, School of Medicine
Role in study	Co-investigator
Training/qualification in research ethics	Research ethics training appropriate to grade completed, GCP completed
Research Integrity Training	Research Integrity courses have been completed
UoN Code of Research Conduct and Research Ethics	Yes
title and name, qualifications, job title	Dr. Farah Hussain, Ph.D
Department/institute name	Precision Imaging Beacon, Mental Health and Clinical Neurosciences, School of Medicine
Role in study	Project Manager
Training/qualification in research ethics	
Research Integrity Training	
UoN Code of Research Conduct and Research Ethics	

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1. SYNOPSIS

Please state why this study is not considered a clinical trial	This study is not designed as a clinical trial and does not aim to assess the effectiveness of an intervention. No NHS patients, premises, staff, equipment or other resources will be involved. Participants will be healthy volunteers, not people with a health condition.	
List all sites where this study will be conducted	- University Park, Nottingham NG7 2RD - Sir Peter Mansfield Imaging Centre – University of Nottingham (University Park & QMC sites) - Nottingham University Hospitals NHS Trust, Queens Medical Centre, Nottingham NG7 2UH	
Age range of study participants	Aged 18 to 40 years	
Planned sample size and groups	The participants recruited for the study will be 30, based on G*Power and effective sample size used by previous studies.	
Planned study duration	1 year	
Anticipated start date	07/2026	
Anticipated end date	12/2027	
	Objectives	**Outcome Measures**
Objectives and outcome measures	To observe the effects of closed-loop non-invasive stimulation on biomarkers of healthy volunteers	Effectiveness on cognitive and physiological biomarkers
Name of drug/ substance/ intervention	- Low intensity focused ultrasound stimulation (FUS) with 500kHz transducer with continuous theta burst protocol using the NeuroFus PRO system - Transcranial electrical stimulation (by means of transcranial alternating current stimulation (tACS) or non-invasive temporal interference (TI) electrical stimulation) using the DS5 isolated bipolar constant current stimulator together connected to a wave generator and with two 9cm2 square electrodes for tACS (TI implementation will be carried out with two DS5 systems, separate wave generators and four 2cm round electrodes). - MRI	
Purpose of drug/ substance/ intervention use in this study	To entrain cortical excitability and enhance the effects of the chosen neurostimulation technique (FUS), increasing the efficacy and reducing the variability of non-invasive stimulation compared to open-loop approaches	
Adverse reactions and side effects posing a particular risk with this treatment	Focused ultrasound stimulation has been extensively tested and found safe and painless. This procedure has received positive ethics previously, as in F1470R and other studies in the School of Psychology. This procedure has shown to have a temporary effect of increasing or decreasing brain cell activity, with no long-term effects. This procedure requires the application of ultrasonic gel on the scalp. If participants have an undiagnosed allergy to the ultrasound gel or one of its ingredients, this may result in an allergic skin reaction. Allergies to ultrasonic gel are rare and tend to present as skin irritation or mild rash that resolves within hours or days. Allergic reactions to ultrasonic gel do not require any clinical intervention.	

	Participants will require an MRI as part of this procedure, which is considered biologically safe. We scan at field strengths of up to 3T. We will be following strict national safety guidelines which are designed to prevent the potential hazards of MRI which are burns and electric shocks. Preventable accidents like skin burnt at the contact point have never occurred in the Sir Peter Mansfield Magnetic Resonance Center (SPMMRC) and have only very rarely occurred elsewhere in the UK. While there is no evidence to suggest that MRI is harmful during pregnancy, the Medicines and Healthcare products Regulatory Agency (MHRA) advises against scanning pregnant women in the first three months of pregnancy or at fields above 2.5T, so we will exclude pregnant women from the study. As part of this procedure, we will also apply electrical stimulation (tES), which involves applying gel to the participant's head and attaching electrodes in conductive gel such as Ten20. This procedure has been widely used in research for over a decade and have received positive ethics previously at the School of Psychology. No serious adverse effects have been reported. Currently, the only known risks are skin irritation for participants with sensitive skin or open head wounds. While participants are being stimulated, they may experience an itching, tingling, or burning sensation. Electroencephalography (EEG) is a painless, comfortable and generally very safe non-invasive procedure, with no side effects considered, as described by NHS. No adverse effects have been reported. The only known risks are temporary skin irritation and redness from the electrodes and skin allergy reactions for participant with undiagnosed allergy to conductive gel.

2. ABBREVIATIONS

ACC	Anterior Cingulate Cortex
DLPFC	Dorsolateral Prefrontal Cortex
dMRI	Diffusion Magnetic Resonance Imaging
EEG	Electroencephalography
FMHS	Faculty of Medicine & Health Sciences
fMRI	Functional Magnetic Resonance Imaging
FUS	Focused Ultrasound Stimulation
GCP	Good Clinical Practice
GP	General Practitioner
ICF	Informed Consent Form
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
PI	Principal Investigator
PIS	Participant Information Sheet
REC	Research Ethics Committee
SOP	Standard Operating Procedure
SPMIC Sir	Peter Mansfield Imaging Centre
tACS	Transcranial Alternating Current Stimulation
tES	Transcranial Electrical Stimulation
TI	Temporal Interference Electrical Stimulation
TMS	Transcranial Magnetic Stimulation
UoN	University of Nottingham
ZTE	Zero Echo Time

3. BACKGROUND AND RATIONALE

Background: Cognitive impairments are a central feature of neuropsychiatric disorders and strongly affect quality of life and daily functioning [1]. Developing effective neuromodulation strategies can reliably improve cognition and therefore remains a major clinical interest. However, current non-invasive brain stimulation techniques, such as transcranial magnetic stimulation (TMS), show substantial variability in their effects across individuals. One likely contributor factor to this is that most of these stimulations involve an open-loop approach in which individuals will all receive identical stimulation, without reference to current brain events.

Recent evidence strongly suggests that the efficacy of these interventions can be increased, and variability of its effects substantially reduced, by adopting a closed-loop strategy, in which stimulation is time-locked to ongoing physiological events within the brain [2]. Brain rhythms can be externally entrained using electrical stimulation, such as transcranial alternating current stimulation (tACS), and latest evidence shows that the excitability effects of TMS can be enhanced when the stimulation is coupled with the phase of these oscillations [3-5].

Transcranial focused ultrasound (FUS) is an emerging non-invasive stimulation technique that has been proven to have fewer side effects compared to well-established neuromodulation approaches like TMS [6] and that have already shown its potential to improve mood and depression scores [7] and reduce symptoms in schizophrenia patients [8] through its ability to stimulate deep-brain structures.

Although electrical stimulation such as tACS cannot directly reach deep structures, it can entrain cortical networks that are functionally connected to them. Therefore, entraining the left dorsolateral prefrontal cortex (DLPFC) rhythms may influence deeper regions such as the left anterior cingulate cortex (ACC). This way, combining tACS with FUS could provide an effective and non-invasive way to develop a closed-loop personalised stimulation.

Aims: To establish non-invasive closed-loop neuromodulation as an effective approach to enhance cognitive function, which could lead to its establishment as an effective intervention for neuropsychiatric disorders such as depression and schizophrenia.

Closed-loop approaches may offer greater efficacy and lower variability across individuals compared to current open-loop stimulation approaches, yet they remain a relatively new approach, with not many studies evaluating closed-loop TMS, and no studies evaluating closed-loop FUS yet.

For this reason, we will collect and evaluate cognitive, biological and metabolic data from healthy participants, before and after closed-loop and open-loop stimulation interventions. This will allow us to compare our proposed closed-loop stimulation approach to stablished non-invasive techniques and to investigate the underlying mechanisms through which FUS can alter brain activity.

A key innovation of this study is the first human evaluation of a closed-loop FUS protocol that aligns stimulation with specific brain oscillations. We will also assess whether closed-loop FUS can specifically engage with excitatory or inhibitory neural populations in the target structure using MRS.

Finally, the collected multimodal brain imaging data will support the development of novel predictive models of stimulation outcomes. By integrating connectome-level analyses and computational modelling, we aim to identify the structural and functional pathways through which FUS have direct and indirect effects on brain activity.

References:

1. Gold, J. M. (2004). Cognitive deficits as treatment targets in schizophrenia. *Schizophrenia research*, *72*(1), 21-28.
2. Zrenner, C., Desideri, D., Belardinelli, P., & Ziemann, U. (2018). Real-time EEG-defined excitability states determine efficacy of TMS-induced plasticity in human motor cortex. *Brain stimulation*, *11*(2), 374-389.
3. Nakazono, H., Ogata, K., Takeda, A., Yamada, E., Oka, S., & Tobimatsu, S. (2021). A specific phase of transcranial alternating current stimulation at the β frequency boosts repetitive paired-pulse TMS-induced plasticity. *Scientific reports*, *11*(1), 13179.
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5. Raco, V., Bauer, R., Tharsan, S., & Gharabaghi, A. (2016). Combining TMS and tACS for closed-loop phase-dependent modulation of corticospinal excitability: a feasibility study. *Frontiers in cellular neuroscience*, *10*, 143.
6. Sarica, C., Nankoo, J. F., Fomenko, A., Grippe, T. C., Yamamoto, K., Samuel, N., ... & Chen, R. (2022). Human studies of transcranial ultrasound neuromodulation: a systematic review of effectiveness and safety. *Brain stimulation*, *15*(3), 737-746.
7. Reznik, S. J., Sanguinetti, J. L., Tyler, W. J., Daft, C., & Allen, J. J. (2020). A double-blind pilot study of transcranial ultrasound (TUS) as a five-day intervention: TUS mitigates worry among depressed participants. *Neurology, Psychiatry and Brain Research*, *37*, 60-66.
8. Zhai, Z., Ren, L., Song, Z., Xiang, Q., Zhuo, K., Zhang, S., ... & Liu, D. (2023). The efficacy of low-intensity transcranial ultrasound stimulation on negative symptoms in schizophrenia: a double-blind, randomized sham-controlled study. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation*, *16*(3), 790-792.

4. PARTICIPANTS

Description of study participants

30 healthy volunteers aged 18 or over

Inclusion criteria

- Participant is willing and able to give informed consent for participation in the study
- Aged between 18 and 40
- Good general health
- Not consume alcohol 48 hours prior study visit
- Not currently taking any medications (except contraceptive pills) or if on long-term medication for a non-neurological/non-psychiatric condition (r.g. inhalers) to be considered otherwise healthy and stable with no symptoms
- Be right handedness

Exclusion criteria

- Inability to complete MRI/FUS /tES safety questionnaire and / or informed consent process.
- Current or previous diagnosis of a neurological, neurosurgical, psychiatric disorders.
- Other significant medical condition (specific details to be reviewed by the CI prior to inclusion).
- Currently pregnant, breast feeding, or on planned pregnancy.
- Medication intake (such as beta-blocker, glucocorticoids, anti-depressants, anti-inflammatory drugs in the last 7d).
- Medication intake (such as antidepressants, antipsychotics, anti-epileptics, beta blockers, glucocorticoids, anti-inflammatories, benzodiazepines, hypnotics, sedating antihistamines or any illicit substances in the past seven days).
- Excessive consumption of alcohol or drugs.
- Known allergy to any required consumables (such as aquasonic gel).
- History of anaphylaxis to any substance
- Having skin disease or sensitive skin on or close to the head.

Recruitment

Participants will be recruited by word of mouth, emails to departmental mailing lists and posters located on the University premises. Participants will be recruited from adverts (posters and information), distributed to the departmental participant database, placed online, and in buildings around the University of Nottingham (UK campuses e.g. University Park, Jubilee). Interested participants can choose to take part in the study by contacting a member of the study team by email (contact details are provided on all advertising materials). After the participant has contacted the study team, further information will be provided (brief explanation of the study and Participant Information Sheet will be sent by e-mail, and the study team members will assess eligibility.

Screening and eligibility assessment

Specify the maximum duration allowed between screening and recruitment (if applicable).

Participants will be screened for eligibility in accordance with the inclusion and exclusion criteria either verbally or via email. The duration between screening and recruitment will be one month.

Information provided to participants and informed consent

Specify who will take informed consent, how and when it will be taken.

The process for obtaining participant informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. A member of the research team and the participant will both sign and date the consent form before the person can participate in

the study. The participant will receive a copy of the signed and dated forms, and the original will be retained in the master file.

A written PIS will be presented to the participants when they express interest in the study. This PIS will detail the exact practical demands of the study, written from the participant's perspective and in simple non-technical language. The participant will be allowed adequate time to consider the information presented in the PIS, and will have the opportunity to question the investigative team or other independent parties to decide whether they will participate in the study. After agreeing to participate, written informed consent will require a dated signature by the participant and dated signature of the person who presented and obtained the informed consent (Appendix I). The person who obtained the consent must be suitably informed, qualified and experienced, and have been authorised to do so by the PI. A copy of the signed informed consent form will be given to the participant. The original signed form will be retained at the study site file.

List the names and job roles of the investigative team members who will obtain consent:
Alicia Falcon Caro (Research Fellow)
Daniel Halls (Research Fellow)
Stefanos Kontogouris (PhD student)

Participant confidentiality

Give details about how you will maintain confidentiality of participant's personal and research data.

All study staff will ensure that the participants' data are safeguarded. The study will comply with the Data Protection Act, which requires all personal data to be anonymised as soon as it is practical to do so. Where possible, participants will be identified only by a participant ID number on study documents, study samples and on any electronic database. Documents (such as consent forms) that contain identifying data and/or information allowing this to be linked to the participant ID will be stored separately under strict access controls. All documents will be stored securely and only accessible by study staff and authorised personnel. If participants agree for their contact details to be kept for the purpose of inviting them to take part in future research studies, their name, contact details and date of birth will be stored on a separate database under strict access controls. The Data Management Plan will be adhered to at all times.

5. STUDY PROCEDURES

Baseline assessments and procedures

Participants will attend multiple visits. Following safety guidelines, each participant will receive a maximum of two 1-hour MRI scanning sessions in a single week.

This study will be separated into two blocks of stimulation sessions: Closed-loop with tACS and closed-loop with TI peak. Participants will be randomly allocated to receive one of the blocks.

As part of the eligibility assessment, participants will be asked to complete some baseline questionnaires online (such as the O-Life inventory, BECK, MAIA, or STAI) and attend an in-person visit. During the in-person assessment, safety screening will be undertaken and eligibility confirmed using the FUS, tES and MRI safety screening questionnaires and participants will be asked to complete one Visual working memory task. If eligibility is confirmed, informed consent will then be obtained, and Demographic information will be recorded for each participant.

On their then first official visit, participants will then have a brain scan at Sir Peter Mansfield Imaging Centre or Queen's Medical Centre. This will help us to apply the brain stimulation to the right part of the participant's brain, as well as obtain baseline functional, metabolic and structural information. The scan will consist on high-resolution structural and functional scans along with Magnetic Resonance Spectroscopy (MRS) through Magnetic Resonance Imaging (MRI).

Within each block, participants will be randomly allocated to either receive closed-loop FUS, open-loop FUS, tES or Sham FUS in the second appointment and the other interventions in the subsequent visits for their assigned block. For all stimulation sessions, we will use an AntNeuro neuronavigation system to guide the location of our transducer.

During either of the stimulation visits, participants will have physiological (EEG), vital signs (Blood pressure, body temperature and heart rate) and cognitive markers recorded. Some emotional assessments (i.e., through a short STAI) will be performed before and after stimulation. We will record 32-channel whole-head EEG using the system available in Precision Imaging. EEG recordings will be conducted before, during and after stimulation on the same day. Rest-state EEG will be recorded pre-stimulation before the start of the cognitive tasks, and post-stimulation after the end of the cognitive tasks.

The participant will then undergo one cognitive assessment. The task will be completed using PsychoPy. Participants will complete a visual working memory task (delayed-spatial-estimation-task) as an indicator of cognitive improvement. The task involves visual stimuli, with responses recorded via keyboard. The task is designed to take approximately 5-15 minutes to complete on pre and post-stimulation. The duration of the task during stimulation will be adapted to the duration of the stimulation.

This task provide a comprehensive assessment of cognitive functioning and is tailored to measure specific domain influenced by ACC.

Following this, participants will receive the intervention, which will consist of one of the following four options:

1) Closed-loop FUS (Dual FUS and tES): Combining FUS stimulation with the selected tES. After the stimulation and cognitive assessments have been completed, the participant will have a second brain scan. Similar MRI protocol will be followed as in baseline. We will aim at obtaining the brain scan between 15-35 minutes after the FUS stimulation has finished to capture early metabolic changes.
2) FUS with Sham: FUS stimulation will be applied to the target area (left ACC) linked to stimulus presentation.
3) tES with Sham FUS: the selected tES (tACS or TI) will be used to entrain the brain.
4) Double Sham: sham FUS stimulation will be performed while participants complete the cognitive task.

On each session involving tES, before the stimulation, participants will have a brief trial where they will experience what tES feels like to confirm that they are comfortable with this stimulation.

Participants will have the same physiological and cognitive assessments recorded during the stimulation and after the stimulation has been completed. The first visit, consisting of brain scan, will be separated by at least 24 hours from the second visit. Subsequent visits will be separated by at least one week from each other.

During each consecutive appointment, participants will be asked about any changes to their eligibility and continued consent (but eligibility will not be reconfirmed in writing, nor will written informed consent be obtained a second time unless there are undertaking an MRI scan).

24 hours and one week after each stimulation visit participants will be asked to complete an adverse effect questionnaire. At the end of the last study visit, participants will be asked to complete the Effectiveness of blinding and adverse effects questionnaire.

Subsequent visits

Participants allocated to dual FUS-tES at their second visit (first visit consist on MRI scanning), will receive either FUS with Sham tES, tES with Sham FUS or double sham on the third visit, and the remaining interventions at the fourth and fifth visits, and viceversa.

Apart from obtaining demographics and medical history which will only be recorded in the first visit, the subsequent visits will comprise of the same physical and cognitive assessments prior, during and post intervention. During the last visit of each block, the participants will fill out a final adverse effects questionnaire for FUS.

Sample handling

No samples will be collected

Discontinuation/ withdrawal of participants from study

Each participant has the right to withdraw from the study at any time. In addition, the research team may discontinue a participant from the study at any time they consider it necessary for any reason including:

- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with treatment regimen or study requirements
- Withdrawal of consent
- Major health changes between the different visits (for instance substantial change in medication or an operation)
- Pregnancy
- Loss to follow up

If a participant withdraws or is withdrawn from the study, the reason will be recorded. If the participant withdraws from the study, their personal data will be destroyed, but we will keep the anonymous research data that has already been collected and stored. This information may have already been used in some analyses and may still be used in the final study analyses.

If a participant withdraws as a result of an adverse event, one of two courses of action will be followed. Firstly, if the participant withdraws due to discomfort resulting from the stimulation, the device will be turned off, ending the stimulation and therefore the associated discomfort. Secondly, if a participant develops a rash or skin irritation as a result of an allergic reaction to the ultrasound or conductive gel, the participant will be advised to contact their GP or call NHS 111 at their own discretion.

Definition of end of study

The end of participant involvement in the study is the date of the last visit of the last participant.

Expenses and benefits

Participants will receive £100 in Amazon vouchers (£20 per completed stimulation visit) for their participation in this research study upon completion of all visits. Some participants might be invited to additional visits.

If they withdraw from the study for medical reasons not associated with the study, a payment will be made proportional to the length of the period of participation. If they withdraw for any other reason, the payment to be made, if any, shall be at the discretion of the lead investigator. Reasonable travel expenses up to £15 per visit will be reimbursed.

6. INTERVENTION(S) & DRUG ADMINISTRATION

a) Drug/ Substance/ Intervention 1

Name of drug/ substance/ intervention to be used	Focused Ultrasound Stimulation delivered to ACC through the NeuroFUS PRO system
Formulation and route of administration for study	N/A
Dose and route of administration for study	Theta burst FUS (500 kHz transducer) delivered to dACC via NeuroFUS PRO stimulator
Duration of treatment for study	Maximum 5min
Licence status of this drug/substance	N/A
Usual indication	N/A
Usual dose	N/A
Usual duration of treatment	
Where will drug/ substance be sourced from?	*Give name and address of manufacturer and/or supplier.* N/A
Where will drug/substance be stored?	*Give location and storage facility/temperature (room temp, fridge etc).* Ensure that storage is correct for this drug/ substance. N/A
How will drug/substance be dispensed?	N/A
How will the drug/ substance be prepared by the researchers for use in this study?	*Give details of any preparation or modification (such as over-encapsulation).* N/A

b) Drug/ Substance/ Intervention 2

Name of drug/ substance/ intervention to be used	Closed-loop Transcranial Electrical Stimulation by means of tES delivered through a Digitimer DS5 for brain entrainment phase-locked to Focused Ultrasound Stimulation delivered to dACC through the NeuroFUS PRO system
Formulation and route of administration for study	N/A
Dose and route of administration for study	tACS or TI: 1mA peak-to-peak amplitude delivered via Digitimer DS5 stimulator. A 10 seconds ramp will be applied at the beginning and end of the stimulation. Concurrent theta burst FUS (500 kHz transducer) will be delivered to dACC via NeuroFUS PRO stimulator
Duration of treatment for study	Main stimulation will take approximately 5.20 minutes (10 seconds ramp up + 5 minutes stimulation + 10 seconds ramp down).
Licence status of this drug/substance	N/A
Usual indication	N/A
Usual dose	N/A
Usual duration of treatment	
Where will drug/ substance be sourced from?	*Give name and address of manufacturer and/or supplier.* N/A
Where will drug/substance be stored?	*Give location and storage facility/temperature (room temp, fridge etc).* Ensure that storage is correct for this drug/ substance. N/A
How will drug/substance be dispensed?	N/A

How will the drug/ substance be prepared by the researchers for use in this study?	*Give details of any preparation or modification (such as over-encapsulation).* N/A

c) Drug/ Substance/ Intervention 3

Name of drug/ substance/ intervention to be used	Transcranial Electrical Stimulation by means of tES delivered through a Digitimer DS5 for brain entrainment
Formulation and route of administration for study	N/A
Dose and route of administration for study	tACS or TI: 1mA peak-to-peak amplitude delivered via Digitimer DS5 stimulator. A 10 seconds ramp will be applied at the beginning and end of the stimulation
Duration of treatment for study	Main stimulation will take approximately 5.20 minutes (10 seconds ramp up + 5 minutes stimulation + 10 seconds ramp down).
Licence status of this drug/substance	N/A
Usual indication	N/A
Usual dose	N/A
Usual duration of treatment	
Where will drug/ substance be sourced from?	*Give name and address of manufacturer and/or supplier.* N/A
Where will drug/substance be stored?	*Give location and storage facility/temperature (room temp, fridge etc).* Ensure that storage is correct for this drug/ substance. N/A
How will drug/substance be dispensed?	N/A
How will the drug/ substance be prepared by the researchers for use in this study?	*Give details of any preparation or modification (such as over-encapsulation).* N/A

d) Drug/ Substance/ Intervention 4

Name of drug/ substance/ intervention to be used	Sham Focused Ultrasound Stimulation
Formulation and route of administration for study	N/A
Dose and route of administration for study	
Duration of treatment for study	Main stimulation will take approximately 5.20 minutes (10 seconds ramp up + 5 minutes stimulation + 10 seconds ramp down).
Licence status of this drug/substance	N/A
Usual indication	N/A
Usual dose	N/A
Usual duration of treatment	
Where will drug/ substance be sourced from?	*Give name and address of manufacturer and/or supplier.* N/A
Where will drug/substance be stored?	*Give location and storage facility/temperature (room temp, fridge etc).* Ensure that storage is correct for this drug/ substance. N/A
How will drug/substance be dispensed?	N/A

How will the drug/ substance be prepared by the researchers for use in this study?	*Give details of any preparation or modification (such as over-encapsulation).* N/A

7. SAFETY

a) Definitions

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a substance has been administered, including occurrences which are not necessarily caused by or related to that substance.
Adverse Reaction (AR)	An untoward and unintended response in a participant to a substance, which is related to any dose administered to that participant. A causal relationship between the administered substance and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the study intervention qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect. Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the study treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product set out in its summary of product characteristics (SmPC).

a) Reporting Procedures for Serious Adverse Events or Reactions

A serious adverse event (SAE) occurring to a participant should be reported to UoN FMHS UREC where, in the opinion of the PI, the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' (the type of event is not listed on this form as an expected occurrence). Reports of related and unexpected SAE's should be submitted by the PI within 7 days of the event. For fatal and life-threatening SUSARs, this will be done no later than 3 calendar days after the Sponsor or PI is first aware of the reaction. Any additional relevant information will be reported within 7 calendar days of the initial report.

b) Safety of Participants

What level of baseline screening will take place for this study?
Screening will be performed verbally or in writing to assess that potential participants are generally healthy, do not take any medication (excluding oral contraceptives), do not have any implanted materials, and have skin conditions in accordance with the exclusion criteria. Inclusion and exclusion criteria will be strictly verified by the researcher taking the informed consent. Participants will also undergo detailed MRI safety testing as per local protocol, and using the MRI safety questionnaire.
Provide details about the safety monitoring of participants and the staff/researchers carrying this out
Participants will be continually observed by a member of the study team whilst undergoing the intervention. Participants will be encouraged from the moment the device is turned on to describe any and all sensations they experience in general and at the site where the stimulators are located. Participants will be advised that the intervention can be stopped at any time and it will be stopped immediately at their request.

On the other hand, MRI scanning is not painful or invasive and is not dangerous provided standard safety procedures are adhered to. We will be following strict national safety guidelines which are designed to prevent the theoretical hazards of MRI, which are burns and electric shocks. Such accidents have never occurred in SPMICand have only very rarely occurred elsewhere. The MRI scanner is an enclosed space which some individuals may find unpleasant. We would not recommend participation in this project by individuals with claustrophobia. The MRI scanner is also noisy, and we routinely provide ear plugs and headphones to prevent discomfort due to the noise, and to prevent the theoretical risk of damage to hearing.
Give details of the medical cover required and who will provide this cover
No medical cover required.
Will the participants' GP be informed about their participation in the study?
No
What is your planned procedure if an incidental finding is suspected?
As the participants are healthy individuals it is extremely unlikely that any abnormalities will be observed. The study visits will be collecting data for scientific purposes will not be carried out by trained medics. However, if any abnormal EEG are observed then you will be contacted and you will be advised to seek medical advice by an appropriately qualified doctor. The incidental finding of previously undiagnosed allergy to aquasonic gel or one of its ingredients could be revealed. If a participant appears to experience an allergic reaction to the aquasonic gel, the intervention will be halted and the participant advised to ring 111 for advice or make an appointment with their GP. Allergies to the components of aquasonic gel or EEG conductive gel are rare, but the documented reactions are limited to skin irritation, redness and rash. No anaphylactic reaction to any of the ingredients of aquasonic gel have ever been reported to the knowledge of the applicants. In the unlikely event that a potential abnormality is identified on the MRI scan by one of the researchers, the incidental findings policy will be applied. If we find anything abnormal, then the scan will be sent to an appropriately qualified doctor (hospital consultant radiologist) to look at it. If the suspicion of a significant abnormality is confirmed, the findings will be explained to the participant and details of the findings sent to their General Practitioner. The radiologist involved will advise on appropriate measure which will need to be taken considering the findings, which may include performing further scans or referral to an appropriate hospital-based specialist, both of which would be arranged by the participant's General Practitioner. Participants would not be informed unless the doctor considers the finding has clear implications for their current or future health.

c) Ethical Considerations

Most research carries the risk of some ethical challenge. If this is the case you need to demonstrate your awareness of the problem and your response to mitigate ethical objections. There is a free text box below to detail any study specific ethical issues, however the following areas are often a cause for concern:

Will you include any vulnerable participants ? (e.g. children (under 16 years old) or vulnerable adults with a mental incapacity or prisoners) **If yes,** please describe how they are defined as vulnerable and detail any approved procedures or guidance that you feel apply.	Yes ☐	No ☒
Will taking part in the research put participants under any particular burden and/ or risk? **If yes,** describe how this will be mitigated.	Yes ☐	No ☒

Will the research involve deliberate *deception* of participants? **If yes**, justify why deception is used, describe deception and debriefing process, and include debriefing documents in the application.	Yes ☐	No ☒
Will any procedures affect your own or any member of the research teams physical and/ or psychological safety as a researcher? **If yes,** describe how this will be mitigated.	Yes ☐	No ☒
Does your research raise issues relevant to the Counter-Terrorism and Security Act (the Prevent Duty), which seeks to prevent people from being drawn into terrorism? **If yes,** please say how you plan to address any related risks.	Yes ☐	No ☒
Please give details of any other study-specific ethical and/or safety considerations.		
The procedures to be undergone by the participants in the study (MRI scans, questionnaires, neurostimulation, behavioural tasks), do not put the participants at a particular and significant risk, and the inconvenience they entail is deemed to be low.		

8. STATISTICS AND ANALYSIS

Do you have a statistical plan? **If no,** please justify.	Yes ☐	No ☒
This is an exploratory study, during which we develop and evaluate new methodology and protocols.		

Number of participants & group allocations

Thirty participants will be recruited. The participants will be separated in two blocks: block one covering FUS stimulations with tACS and block two covering FUS stimulations with TI. The thirty participants will be randomly allocated to receive either block one or two, with the possibility of receiving the remaining block of stimulation after if they agree. Each block of stimulations will be separated by two weeks.
In each block, participants will undertake an MRI scan on the first visit. The order of the subsequent FUS stimulation visits will be randomised.

Have you done a sample size calculation? If yes, please give details below. If no, please give details to indicate you have considered the implications the selected sample size will have on the study outcome.	Yes ☒	No ☐
Yes, the sample size was obtained through a G*Power calculation.		

Analysis of Outcome Measures

The questionnaires will be scored, and descriptive statistics will be calculated. Behavioural and physiological data will be scored and paired t-tests will be used to compare before and after stimulation results and post-stimulation results with post-sham results. Physiological data will be evaluated through well-stablished analysis methods as well as novel techniques that might be implemented. Acceptability will be tested using a t-test comparing scores obtained after closed-loop FUS to scores obtained after sham FUS and open-loop FUS. Effectiveness of blinding will be statistically tested using James's Blinding Index.

9. DATA MANAGEMENT

It is now a University governance requirement that every research project has a **Data Management Plan (DMP)**: Here is the link to Digital Research for information and training: DMP

Summary for Form

Who will have access to the *research* data?	The study research team will have access to the data. Any data which leaves the research unit will have identifiable personal information removed so that participants cannot be recognised from it. Some participant personal data, which may include email addresses and study identity code number, may be shared with Connectome Health GmbH for the purposes of managing participant profiles and supporting the study. This information may be stored or processed in the UK and Switzerland, subject to appropriate data protection safeguards. Personal details will not be passed onto any third parties other than those involved in the study's approved data processing arrangements. Anonymised data may also be stored indefinitely on external data repositories (e.g., https://openneuro.org) and be further processed for archiving purposes in the public interest. Direct access will be granted to authorised representatives from the University of Nottingham and any host institution for monitoring and/or audit of the study to ensure compliance with regulations.
How will *research* data be stored?	Each participant will be assigned a study identity code number for use on all study documents, questionnaires and electronic database. The documents and database may also use their initials (of first and last names separated by a hyphen or a middle name initial when available) and date of birth (dd/mm/yyyy). All study documents will be treated as confidential documents and held securely in accordance with regulations. Electronic data will be stored on secure, access-controlled systems, with appropriate password protection and encryption where applicable.
How long will *research* data be stored for?	The University minimum retention period for research data and records is 7 years after the end of the study. Research data held or processed by Connectome will be retained in accordance with the agreed data retention arrangements.
What will be done with the *research* data at the end of the storage period?	At the end of the storage period, data will be destroyed by the PI and trained University/BRC staff in accordance with UoN policy. Data held by Connectome will be securely deleted or returned, as applicable, in accordance with the agreed data retention and deletion arrangements.
Who will have access to the participants' *personal* data?	The PI will have access and grant access to specific BRC staff for the purposes of data management and transcription. Authorised personnel at Connectome may also access or process the personal data necessary to provide the platform services for the study.
How will *personal* data be stored?	Any documentation with identifiable (personal) data will be stored securely and separate from the research data The contact details of participants will be kept on a separate file on the secure UoN server. Each participant will be assigned a study identity code number (EG US01) for use on all study

	documents and the electronic database. The documents and database may also use their initials (of first and last names separated by a hyphen or a middle name initial when available) and date of birth (dd/mm/yyyy). Connectome may also hold participant's email addresses and study identity code number where required to manage participant profiles. Such data may be stored or processed in the UK and Switzerland. Appropriate technical and organisational safeguards, including access controls and other applicable security measures, will be used to protect personal data against unauthorised access, loss or disclosure.
How long will *personal* data be stored for?	To comply with the data protection act, personal data will be deleted as soon as possible after it is no longer needed for the study. Personal data held by Connectome will be retained only for the duration of the study and in accordance with the agreed retention arrangements.
Describe method(s) of research data entry/management	All study data will be entered on Excel spreadsheets. The participants will be identified by a unique study specific number and/or code in any database. Where Connectome is used, relevant participant data will be processed through the platform in accordance with the study's approved data management arrangements. Please see data management plan for further details.

10. STUDY MONITORING AND OVERSIGHT

Who will be responsible for day-to-day supervision of the study?
Professor Marcus Kaiser
Give information about frequency of meetings that will be held to discuss progress/problems. Who will be present at the meetings?
Weekly study meetings will be held between the ERC Research fellows and the PI to discuss progress of the study. Monthly meetings will be held within the study team.

11. ETHICAL AND REGULATORY CONSIDERATIONS

Declaration of Helsinki

The PI will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

Approvals

This form, an informed consent form, a participant information sheet(s) and any proposed advertising material will be submitted to the UoN FMHS REC for written approval. The research team will submit and, where necessary, obtain approval from the UoN FMHS REC and any other above-mentioned parties for all amendments to the original approved documents.

End-of-Study Report

The PI shall request, complete and submit an end-of-study report to the UoN FMHS REC within 6 months of the study end (participant involvement).

12. INSURANCE AND INDEMNITY

This section may require amendment depending on your study as there are exclusion criteria within the University's policies. Please contact the UoN Insurance Team or Supervisor for advice.

Insurance and indemnity for University employees, its agents and students conducting University business is provided through several policies.

13. DISSEMINATION AND FEEDBACK OF STUDY OUTCOMES

Please describe your plans with respect to participants as well as public dissemination plans, e.g. in journals and conferences. If the study results form part of a Masters or DPhil dissertation, please give details here. Consider describing how study results may be disseminated to study participants.

14. REFERENCES

Insert references used in text in number or alphabetical order (excluding those already listed in Section 4).

15. DECLARATIONS AND SIGNATURES

I/ we, the researcher(s) agree:

- Understand our responsibilities in line the University of Nottingham Code of Research Conduct and Research Ethics and UoN Policies and Guidance
- To start this research study only after obtaining approval from the UoN FMHS REC
- To carry out this research study only if funding is adequate to enable it to be carried out according to good research practice and in an ethical manner
- That it is the responsibility of the PI to ensure that all researchers working on this project are qualified and either experienced, or have received appropriate training (including ethical training), to conduct the research described;
- To provide additional information as requested by UoN FMHS REC before approval is secured and as

research progresses

- To maintain the confidentiality of all data collected from or about study participants
- To notify UoN FMHS REC in writing immediately of any proposed change which would increase the risk or burden that any participant is exposed to, and await approval before proceeding with the proposed change
- To notify UoN FMHS REC if the PI on the study changes and supply the name of the successor;
- To notify UoN FMHS REC in writing within seven days if any unexpected or serious adverse event occurs in the course of research
- To use data collected only for the study for which approval has been given;
- To grant access to data only to authorised persons
- To maintain security procedures to ensure that personal data collected from participants will be held in compliance with the requirements of the GDPR and the Data Protection Act 2018.

Principal Investigator (Name)	Marcus Kaiser
Principal Investigator (Signature)	
Medically qualified collaborator (Name)	N/A
Medically qualified collaborator (Signature)	N/A
Student (Name)	N/A
Student (Signature)	N/A

16. Useful links:

1. Code of Research Conduct and Research Ethics https://uniofnottm.sharepoint.com/sites/ResearchEthicsandIntegrity/SitePages/Code-of-conduct.aspx
2. Reading the following Code of Practice for Research Ethics Committees should give you a clear understanding of the review criteria used to assess research projects and help you plan your study. Code of Practice for Research Ethics Committees
3. UKRIO Recommended Checklist for Researchers
4. Access and Benefits Sharing and Nagoya Protocol
5. UoN Information Security and Compliance Team – for advice on using personal data and GDPR https://uniofnottm.sharepoint.com/sites/InformationSecurityandCompliance/
6. Research Misconduct
7. International Research and Research Ethics Research Conduct in an International context
8. Research Integrity Bytes: one pagers addressing common issues and questions raised by researchers in all fields. The bytes are written to give researchers a starting point when considering issues that may impact the integrity of their research.
9. Research projects involving NHS patients and/or staff and/or their data: see the Research Governance workspace pages
10. Create a secure online survey https://uniofnottm.sharepoint.com/sites/DigitalResearch/SitePages/Surveys.aspx
11. Automated Transcription Service https://uniofnottm.sharepoint.com/sites/DigitalResearch/SitePages/Automated-Transcription.aspx
12. Cyber Essentials Secure SharePoint https://uniofnottm.sharepoint.com/sites/DigitalResearch/SitePages/Secure-SharePoint--Cyber-Essentials.aspx
13. Digital Research Planning, Data storage, Process & analyse, Promote & archive.
14. Insurance Team: https://uniofnottm.sharepoint.com/sites/Insurance2