Report

Brain Stimulation Safety

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1 Introduction

This document aims to provide a comprehensive overview of the brain stimulation techniques that will be used in 1) the Neural Modulation (NeMo) Laboratory in the School of Psychology research facility at the University of Plymouth and 2) the non-invasive Brain stimulation (NIBS) Laboratory at the Brain Research Imaging Center (BRIC). This document will serve as a guide to general safety and procedures in the NeMo and the NIBS labs and will serve as a resource for training and reference for the experimenters in the two facilities. This document will be periodically reviewed by the Neuro-Stimulation Governance Committee (NSGC) and updated in accordance with safety developments in the field.
There are several techniques for the non-invasive stimulation of the human brain. The aim of these techniques is to modulate the function of specific brain regions with the intention of modifying cognitive and behavioural performance. There are three principal techniques for non-invasive brain stimulation: transcranial magnetic stimulation (TMS), transcranial electrical stimulation (tES) and transcranial ultrasound stimulation (TUS).

1.1 Transcranial Magnetic Stimulation (TMS)

TMS is a technique in which strong electrical currents are used to generate an accompanying magnetic field, which is local to the stimulating coil device. When held in close proximity to the surface of the head, this magnetic field generates a brief secondary current in the neurons of the brain region within a few centimetres of the strongest part of the field causing them to fire. Changing the strength of the electrical current that is passed through the coil can modify the strength of the field and therefore the strength of the stimulation (the number of neurons activated). The brain location that is stimulated is determined by the location and orientation that the coil is positioned against the side of the head.
There are two types of stimulation that can be used, which require two different types of stimulator. The first is brief stimulation, which is delivered by a single pulse TMS system and the second is a sustained pattern of stimulation delivered by a repetitive TMS (rTMS) system.

Figure 1. The brain stimulation laboratories at the University of Plymouth. The left image shows the single pulse TMS equipment (Magstim 200) and the right image shows the rTMS equipment (Magstim Super Rapid).

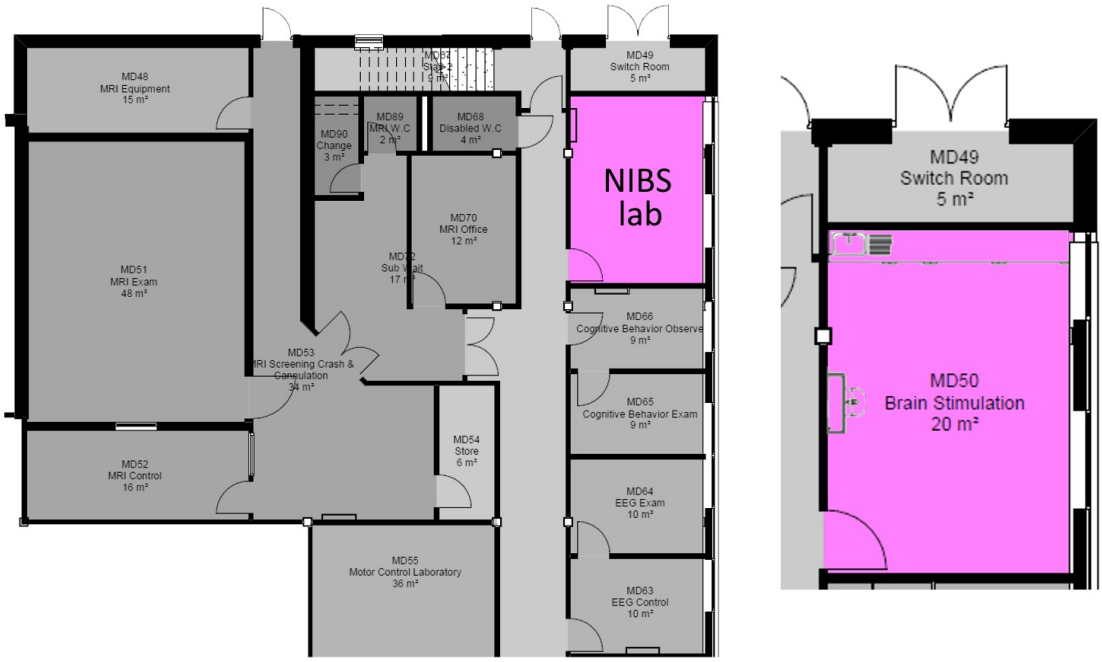

Figure 2. **The NIBS lab at BRIC**. The left image shows the location of the NIBS lab at BRIC and the right image shows more details on the lab.

1.1.1 Single Pulse TMS

Single pulse TMS produces a single short-lived flow of current in the neurons of a particular location in the brain. These neurons fire producing an immediate short-lived affect that does not outlive the period of stimulation by more than 200 milliseconds. This technique can be used as a method of generating a specific output in the motor system, from which an assessment of brain-motor function can be made. Alternatively, it can be used to provide time-specific interruption of brain processes, to determine the important time window in a specific process.

1.1.2 Repetitive TMS (rTMS)

rTMS is used to produce a repeated train, or specific pattern of stimulation. This approach can be subdivided into short-acting and long-acting. The short acting paradigms use a specific frequency of stimulation, typically between 1 and 20Hz that is applied during the performance of a particular task, in a similar manner to single pulse TMS. The duration of this type of stimulation is usually in the order of a few seconds on each trial and the effects do not outlast the period of stimulation by more than 200 milliseconds. The long-acting paradigms aim to produce an effect that is sustained beyond the period of stimulation. This is achieved with two principal approaches:

Sustained frequency stimulation, uses a specific frequency of stimulation (often 1-10Hz) delivered for up to 20 minutes. This approach can provide modulation of function approximately equal to the duration of stimulation (i.e. 20 minutes of stimulation will

produce a 20 minute effect following completion of the stimulation).

Patterned stimulation, uses a physiologically relevant pattern of stimulation to produce modulation of neural activity beyond the duration of stimulation. A common implementation of this is theta burst stimulation (TBS), which uses burst of three 50Hz pulses, four times per second. A 40 second train of stimulation can modulate neural activity for up to one hour.

1.2 Transcranial Electrical Stimulation (tES)

tES approaches are direct electrical stimulation approaches that deliver a small electrical current (1-2mA) via electrodes placed on the surface of a participants scalp. The current delivered using these approaches are spread over a more diffuse area than the TMS approaches because of the nature of current flow compared to magnetic field flux. tES is usually delivered through two electrodes (an anode (+ve) and a cathode (-ve)), although multiple electrodes can be used to direct the current more focally. Unlike TMS, tES does now cause the neurons to fire, but changes the membrane potential of the neurons in the region of the electrodes. There are two types of tES approach, called transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS).

1.2.1 tDCS

tDCS uses a constant current that remains changed at a constant level for the duration of the stimulation. Therefore, dependent upon whether the current is positive or negative over the site of stimulation, the intrinsic firing of the neurons is either increased or decreased in probability.

Figure 3. Direct current stimulation. Schematic of the pulse profile, showing constant delivery during “on” period.

1.2.2 tACS

tACS delivers a sinusoidal current at a specific frequency, which changes the probability of firing of the local neuronal population at a specific frequency.

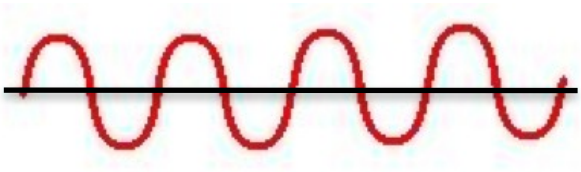

Figure 4. Alternating current stimulation. Schematic of the pulse profile, showing oscillatory delivery over time.

1.3 Focused Transcranial Ultrasound Stimulation (TUS)

Pulsed Focused Low-Intensity Transcranial Ultrasound Stimulation (TUS) uses ultrasound waves that pass through the skull non-invasively and can be focused in three dimensions in a highly targeted manner anywhere in the brain to modulate neural activity at focus. Compared to other stimulation techniques (TMS or tES), the technique holds two promises: 1) a better spatial resolution and 2) the ability to reach deep brain structures. The TUS technology uses a transducer (Fig5, left image) to produce the ultrasound field that reach a targeted zone (Fig5, right images).

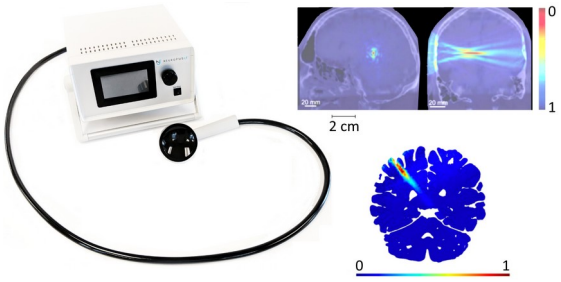

Figure 5. Hardware and simulated propagation. TUS hardware (NeuroFUS–BrainBox) on the left image. Examples of simulated ultrasound wave propagations on individual MRI to focus the ultrasound sonic wave on the thalamus (right top) and of the motor cortex (right bottom image).

1.3.1 Ultrasonic waves

The principles of TUS builds upon the properties of waves. Typically, ultrasound are made of *longitudinal waves* such that molecules travel along the direction of compression and rarefaction (Fig6). Ultrasound use frequencies that are above the upper audible human ear limit (> 20 KHz).

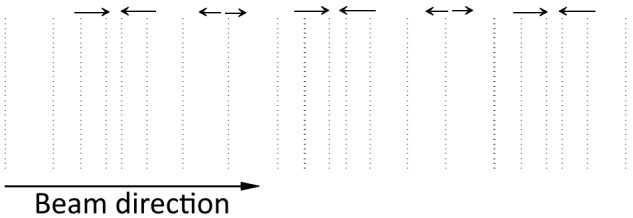

Figure 6. Characteristics of longitudinal waves.

1.3.2 Focused beam

The ultrasonic waves can be focused (contrary to diagnostic ultrasound - like in pregnancy - where the beams are unfocused and eventually diverged from the near field path) in order to create a beam's focal point and thus a narrow area of high resolution (in the millimetric precision), called the focal zone. It is only in the focal zone that neuromodulation is observed.

1.3.3 Low intensity

Low intensity ultrasound can be divided in two main categories: 1) Diagnosis imaging and 2) TUS.

- With 1) diagnostic imaging, a transducer transmits unfocused ultrasound and their reflection is used to create an image of different tissues. It does not *induce* any biological effect. The safety of ultrasound pulses for diagnostic imaging has been extensively studied (Duck 2008). Three metrics are typically quoted to ensure the safety of the incident US pulse: intensity, thermal index (TI) and mechanical index (MI).
- With 2) TUS, a transducer transmit focused ultrasound (see section 1.3.2) and induce *reversible* effect. TUS relies on ***mechanical effects*** (non-thermal) that are described on section 1.3.6 and 1.4.3.

1.3.4 High intensity

At high intensities, with focused beams and continuous delivery (high-intensity focused ultrasound, HIFU) ultrasound can heat soft tissues leading to thermal ablation or fraction of the tissues. While HIFU protocols exceed 200 W/cm^2, TUS protocol intensities similar or lower than the one used for imaging (<<100 W/cm^2).

1.3.5 Pulsed delivery

Not all ultrasound delivery create neuromodulation effects. These are observed only when the TUS is administered in focused and (relative to diagnosis imaging) ***longer pulsation mode***, modulating neural responses (this has been reported with EEG and fMRI) and associated behaviors. While diagnostic ultrasound comprises brief pulses of higher frequency (in the MHz range), TUS typically rests on longer pulses at lower frequencies (in the sub-MHz range). All parameters are summarized in details in section 4.4. Note that a pulsed mode is also a main difference with HIFU, which is delivered as a continuous high intensity wave.

1.3.6 Reversible change of neural activity

The effect of TUS neuromodulation lasts from several minutes to a couple of hours after stimulation duration lasting generally less than a minute. This includes reduction of EEG up to 80% and associated BOLD response (Yoo et al., 2011), decrease in in extracellular GABA level (Yang et al., 2012), changes in connectivity profile in rsfMRI (Folloni et al., 2019; Verhagen et al.,

2019), behavioral and motor responses (Baek et al., 2018; Fouragnan et al., 2019).

1.4 Mechanisms of TMS, tES and TUS

There are important differences between the mechanisms of TMS, tES and TUS, which have implications for their application and safety considerations:

1.4.1 Mechanisms of TMS

TMS is a technique that elicits a strong electrical current in a focal population of neurons in the cortex, with an immediate onset linked to the sharp rising edge of the current passed through the coil. The result of this is, above a particular threshold (e.g. motor threshold), the firing of a proportion of the neurons in that population. As a result, TMS used above this threshold is designed to generate focal firing of the neuronal population.

1.4.2 Mechanisms of tES

tES is a technique that introduces a diffuse and therefore relatively weak electrical current to the cortex. Both tDCS and tACS typically have a ramped onset (i.e. not immediate). The combination of a weak electrical current and ramped onset, results in a change in the membrane potential of the population of neurons in the stimulated area (Nitsche and Paulus, 2000).

1.4.3 Mechanisms of TUS

TUS is a technique that propagates pulsed ultrasonic waves through the skulls and tissues. At focus, the interaction between TUS and neurons relies on the ***mechanical*** properties of the membrane although its precise mechanism-of-action is still unclear. Two main models have been proposed (among others), presented in the figure 7 below whereby TUS transiently changes the membrane gating kinetics through actions on voltage-gated channels.

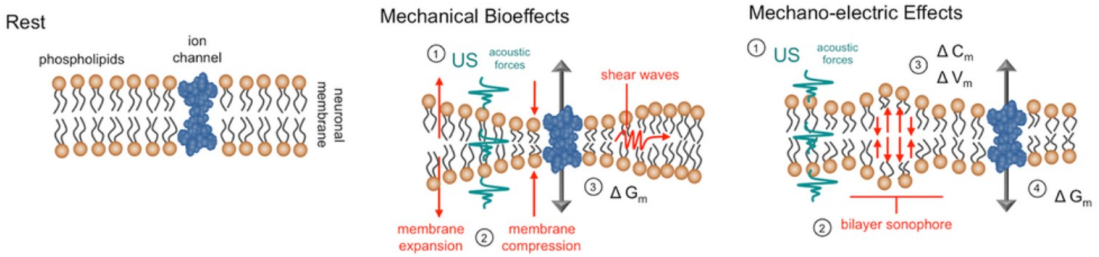

Figure 7. The left panel shows a neuronal membrane at rest. The middle panel represents the first model where the TUS acoustic force [1] causes mechanical effects on the membrane [2] which consequently changes the membrane conductance (Gm) and its resulting neural activity [3]. The right panel shows another model where the TUS acoustic forces causes the formation of a bilayer sonophore [2] that causes displacement currents [3] which changes the membrane capacitance (Cm) and voltage (Vm). These actions consequently alter Gm (adapted from (Tyler et al., 2018))

Additionally, depending on stimulation parameters, TUS can suppress (longer burst duty cycle) or facilitate (shorter burst duty cycle) neural activity. It is important to note that thermal effects and acoustic cavitation have been ruled out (Pasquinelli et al., 2019).

1.4.3 Consideration for safety

The important difference between these techniques lies in the major safety consideration for the experimental participants, which is risk of inducing seizure. In order to induce a seizure, it is necessary to elicit firing of large populations of neurons, which then becomes self-sustaining and leads to propagation and uncontrolled spread of firing to other areas. Given that tES does not elicit firing at the currents applied, the considerations for protocol are quite different from those used in TMS and TUS.

2 Safety Considerations

There are a number of safety aspects that must be considered in the creation of a suitable environment for the safe use of TMS, tES and TUS. In addition, the experimental protocols require careful consideration to ensure that they are performed within acceptable safety limits. The safety considerations can be subdivided into the three populations of people to whom the techniques may pose a risk: the general (non-experimental) population, the experimenter(s) and the participant(s).

2.1 General (non-experimental) Population

General population refers to individuals that are not involved in the experiment and may be unaware of the experiment and/or the equipment. Considerations for this group are as follows:

2.1.1 Magnetic field exposure

This refers to the exposure of individuals to the magnetic fields generated by the devices used, in particular the TMS equipment. Because the general population will not be within the environment during an experiment, this consideration relates to the placement of the device within the experimental room, to ensure that the magnetic fields outside of the room do not expose the general population to prolonged or high-level magnetic fields. The magnetic field decays quickly with distance, such that the magnetic field is electrically inactive (unable to elicit neuron firing) at a few centimetres from the peak field. The field is estimated to be equal to the general ambient field at a distance of 0.7 metres.

Safety strategy

The active TMS coil will be kept at a minimum distance of 0.7 metres from any external wall of the Neuromodulation Laboratory.

2.1.2 Electrical current

1. There is, as with any piece of electrical equipment, a risk posed by the electrical currents that the TMS and TUS machines use. All of the machines operate using mains voltage electricity, directly connected to the mains sockets. The rTMS system has four current booster modules, which are housed in a specialised cabinet. The TUS equipment is similar to a Doppler used in imaging (for example in pregnancy) where covers and protections shield the electrical

components. There are no hazard unless there is damage to the equipment.
2. The tES machine is designed to deliver a low amplitude electrical current under experimental conditions. This current is low-level (1-2mA), delivered by a 9-volt internal battery and poses a minimal risk upon accidental contact. The TMS machine produces a magnetic field, which can generate a local electrical current in biological tissue (<1mA) and poses minimal risk upon accidental contact. However, both the tES and TMS systems are approved medical devices and, accordingly, have safety features incorporated to avoid accidental activation. The tES requires programme selection and acceptance to be activated and the TMS system requires three stage power activation and for depression of a safety switch for activation.

Safety strategy

1. All electrical equipment will be annually PAT tested and marked accordingly. Equipment will be switched off at the mains supply when not in use. Safety features will be tested at regular intervals (proposed 1-month) and recorded in a log.
2. Access to the laboratory will be restricted by key card access, to be permitted to approved users and supervised persons. Appropriate signage will be placed at the outer and inner doors to the laboratory.

2.1.3 Ultrasound exposure

This refers to the exposure of individuals to the ultrasonic fields generated by the TUS devices used. Because the general population will not be within the environment during an experiment, this consideration relates to the placement of the device within the experimental room. The ultrasonic fields depend on the size, form and frequency of the signal source generated by the transducer. Within the conventional parameter ranges used with focused TUS, the ultrasound fields are not more than few centimetres away from the transducer. Moreover, the neuromodulation effect are only observed in the focal zone. To calculate the distance between the focal zone and the transducer (e.g. the depth of focus), we can use the diffraction theory: the depth of focus is proportional to the Aperture of the transducer and the Wavelength. Decays quickly with distance, such that it is unable to interact with human tissue unless placed more than ~20cm centimetres from people.

Safety strategy

The active transducer will be kept at a minimum distance of 1 metre from any external wall of the Neuromodulation Laboratory.

2.1.4 Medical Devices

Devices that generate magnetic fields pose a particular risk to individuals that have implanted medical devices, such as a cardiac pacemaker. The interference with the functioning of these devices means that steps should be taken to minimise the risk of exposure.

Safety Strategy

Appropriate signage will be placed at the entrance to the laboratory to warn against persons with these devices entering the laboratory. Screening procedures will be completed to ensure that people entering the facility for non-experimental purposes (e.g. lab visitors or cleaning staff) are not exposed to magnetic fields if they have implanted medical devices.

2.2 Experimenter(s)

Experimenter(s) refers to the person or people responsible for conducting the experiments in the neuromodulation laboratory. This group will be responsible for safety of the participants in their studies and for ensuring that the laboratory safety strategies are followed during their experimental procedures. Considerations for this group are as follows:

2.2.1 Magnetic field exposure

There is no evidence to suggest that long-term exposure to magnetic fields is associated with any adverse health condition (Rossi et al., 2009).

Safety strategy

Consistent with recommendations for MRI scanning, we will monitor the exposure of experimenters, by means of an experimental log. This will record details of the experimenter, the type of stimulation used, the duration of the experiment and any additional details relevant to the laboratory environment.

2.2.2 Electrical current

Consistent with the points highlighted above (2.1.2), there is a risk posed by the use of electrical devices.

Safety Strategy

Consistent with the strategy described above (2.1.2), electrical equipment will be switched off at the mains after use. Experimenters will be responsible for ensuring that the lab is left in a safe condition before leaving.

2.2.3 Ultrasound exposure

Consistent with the points highlighted above (2.1.3), there is no risk posed by the use of an ultrasound transducer if the beam is not pointed towards the person or kept at a reasonable distance from the experimenters (aside the person manipulating the transducer).

Safety strategy

Consistent with recommendations for MRI scanning and TUS/TES stimulation, we will monitor the exposure of experimenters, by means of an experimental log. This will record details of the experimenter, the type of stimulation used, the duration of the experiment and any additional details relevant to the laboratory environment. In addition, the experimenter will ensure that the beams are not pointed towards her/himself at any time when manipulating the device.

2.2.4 Projectile risk

When placed in close proximity to metallic objects, strong magnetic fields have the capacity to have a projectile effect of the metallic object. This is a particular safety consideration for devices such as MRI scanners, where the field is strong and constant. In the case of TMS, it is possible to elicit a projectile or heating effect upon a metallic object within a few centimetres of the maximal field location. If this occurs there is a risk posed to the experimenter and participant. The TUS is MR compatible, thus there will be no projectile effect from the device.

Safety strategy

Care will be taken to minimise the likelihood of metallic objects coming into contact with the magnetic field generated by the TMS systems. Storage will be provided and experimenters will be required to remove metallic objects such as watches or jewellery before conducting the experiment. Experimenters will be responsible for ensuring that metal objects are removed from their participants by means of the screening process and for checking that there are no hair clips, ear rings, glasses or other metal objects in close proximity to the magnetic field during stimulation.

2.3 Participants

Participant(s) refers to the individuals that take part in the experiments in the NeMo or the NIBS labs. This group will consist of healthy volunteers, recruited from the general population and specific patient groups. Specific considerations will be required for different patient groups and these must be considered in addition to those outlined here. The general considerations for the participant group are as follows:

2.3.1 Magnetic field exposure

Consistent with the points described above (2.1.1 and 2.2.1), the cumulative exposure to magnetic fields will be considered using a similar approach to that applied in the area of MRI safety. Specifically, we will limit the amount of exposure that any individual will receive.

Safety strategy

The amount of magnetic field exposure at experimental strength (i.e. applied directly to the brain) will be limited to a cumulative maximum of 15 minutes of continuous TMS stimulation per month and a maximum of 5 sessions of stimulation over 12 months. This will be determined by means of experimental records in the form of a screening questionnaire, upon which the cumulative stimulation will be listed. Screening forms will be kept in a lockable cabinet within the NeMo and the NIBS labs.

Note: specific patient populations undergo brain stimulation as part of their treatment. These stimulations can be performed over long durations (up to 1 hour) and with high frequency (several times per week). In any study where the exposure conflicts with the cumulative guidelines described above, an individual case should be presented to the NSGC.

2.3.2 Stimulator Noise

The TMS stimulator, when activated, produces a broadband acoustic artefact that can be as great at 140dB. While the impact upon hearing appears to be generally limited to transient shifts in auditory threshold (Rossi et al., 2009), the risk of causing damage should be minimised.

Safety strategy

In experiments where repetitive TMS stimuli will be used (>0.5Hz) for a sustained period (>0.5 seconds), ear protection will be required in the form of earplugs or earmuffs.

2.3.3 Ultrasound exposure

The Food and Drug Administration (FDA) in to this day, regulates ultrasound exposure for neuromodulation. The safety limits for exposure are similar to those used for obstetric diagnostic ultrasound and adult cephalic applications. It is noteworthy that, in four decades that it has been in use, diagnostic ultrasound has produced no harm to participants. However, the parameters used for TUS are different from the ones used for diagnosis. While diagnostic ultrasound comprises brief pulses of higher frequency (in the MHz range), TUS typically rests on longer pulses at lower frequencies (in the sub-MHz range). These two parameters (duration and frequencies) are regulated by FDA guidelines.

A recent safety study (Legon, 2020) gathered data from multiple human TUS studies (more than 120 participants). **The data to date shows that TUS is safe for neuromodulation**. Side effects are similar to those reported in response to other forms of non-invasive neuromodulation (TMS, tES). This study is summarized on figure 8 below.

Additionally, multiple studies have used TUS for neuromodulation in animal models, including rodents, rabbits, sheep, pigs, and non-human primates. These studies report few to no adverse reactions. It is important to note that most of these studies had exceeded the FDA guidelines in terms of TUS parameters.

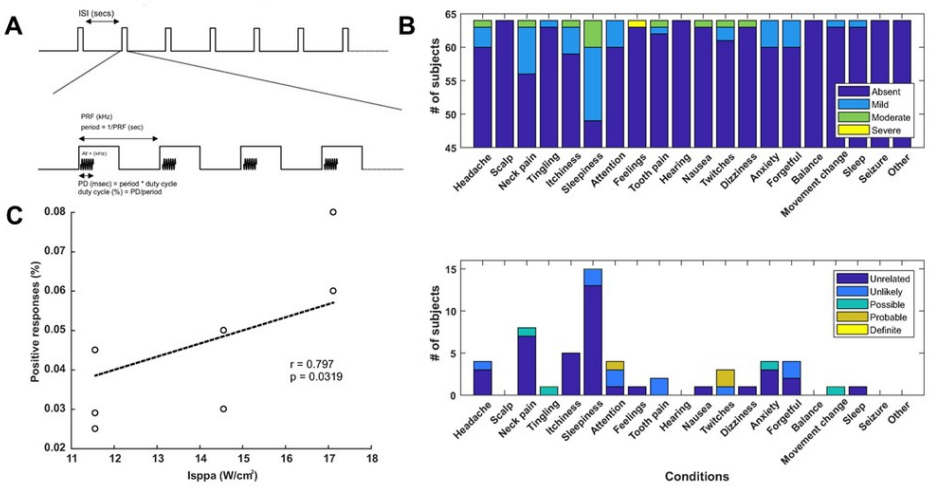

Figure 8. A. TUS protocols for modulating brain activity in the investigated studies. **B**. Histograms illustrating the severity of side effect outcomes (top panel) and outcomes scored by the subjective relation to the TUS treatment (bottom panel). **C**. Scatter plot shows a slight but significant correlation between acoustic intensity (spatial peak pulse average) and the percentage of positive side effect responses.

Safety strategy

We will follow the guideline of the FDA and the TUS parameters limits predicated for neuromodulation (Table 1).

I_{spta} (mW/cm^2)	I_{sppa} (W/cm^2)	MI	TI
720	190	1.9	6

Table 1. Allowed limits for I_{spta}, $I_{sppa,}$ MI and TI, according to the FDA guidelines.

The amount of ultrasound exposure at experimental strength (i.e. applied directly to the brain) will also be limited to a cumulative maximum of 16 minutes of pulsed TUS stimulation per 16 weeks (1 session of 2min maximum every two weeks) and a maximum of 8 sessions of stimulation over 12 months. This will be determined by means of experimental records in the form of a screening questionnaire, upon which the cumulative stimulation will be listed. Screening forms will be kept in a lockable cabinet within the NeMo and the NIBS labs.

Note: In Legon's study (Legon, 2020), authors found a moderate relationship between I_{spta} and response rates (illustrated in panel C figure 8). This suggests that I_{spta} is the most sensitive safety index in case of TUS. We will make sure to always monitor and report $I_{spta.}$

Finally, as the TUS approach is still in its infancy, we will collect ***retrospective data via a Participant Report of Symptoms Questionnaire*** (see appendix) at varying time points post experiment that ranged from 0 months (day of experiment collected in person) to 24 months post experiment (telephone interview).

2.3.4 Local pain, headache and other discomfort

Single pulse stimulation, tDCS and tACS are generally well tolerated and often imperceptible. For TUS, please refer to the section 2.2.3 for a full details on safety and reported side effects. However, because stimulation of the brain requires the passage of magnetic fields through the skull, rTMS protocols may sometimes cause stimulation of the muscles and other tissues. Stimulation of the craniofacial nerves, in particular the trigeminal nerve can cause contraction of the facial muscles or direct perception of local pain. Head immobilisation is likely to be the principal cause of reported neck pain. The occurrence of pain is dependent upon the intensity and duration of the stimulus, the location of the stimulus and the individual participant's perception of pain. Meta-analysis of the occurrence of pain, showed that in high intensity rTMS for treatment of depression (typically high intensity stimulation of more than 15 minutes over the frontal regions), headache was reported in 28% and discomfort in 39% of patients. This was compared to 16% and 15% respectively in sham (fake) rTMS (Loo et al., 2008). In the majority of cases, pain and discomfort is reported to dissipate within a few minutes A recent study across

multiple sites analysed the reports of mild adverse effects (MAE) (summarised in figure 9). They demonstrated consistent reporting of MAEs (no significant difference) between sham (no TMS) and active TMS conditions. They also showed no difference in reported MAEs between different stimulation protocols (Maizey et al., 2013).

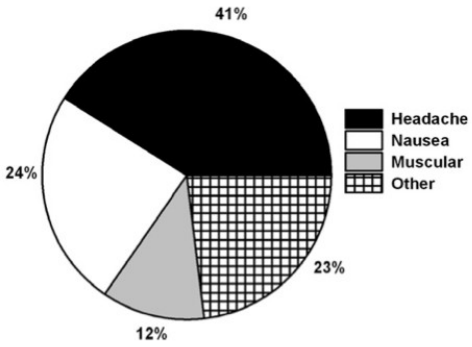

Figure 9. Mild adverse effects. Incidence of mild adverse effects reported by participants following TMS experiments, including sham and active TMS recordings.

Safety strategy

The reported pain during stimulation seems to be associated with protocols of extended duration and high-intensity away from the vertex (centre top of the head). Protocols in the NeMo or the NIBS lab will be limited in duration of stimulation (see section 2.3.4 for current details) and where repeated stimulations are used, efforts will be made to minimise neck strain by allowing movement between trials where possible. In all cases, participant comfort will be assessed throughout the experiments and every opportunity provided for participants to withdraw from the experiment at any stage.

Extra notes:

2- 2- 2-
Immediate reaction to the Covid-19 and future considerations

- check when we need to send he equipment back for certification
- finish the document

Think about the lab website and documents linked to it
Think about first aids updated

3 Risk Groups and other factors

3.1 Pregnancy

Magnetic fields attenuate rapidly with distance and so the risk posed as a result of this is minimal. Indeed, rTMS has been performed on pregnant women, without reported side effects (Klirova et al., 2008). However, there is likely to be an increase in the level of anxiety in this participant population. Additionally, no TUS studies have been conducted with this category.

Safety strategy
A cursory risk/benefit analysis would suggest that under most circumstances there is insufficient basis to include this participant group. If studies wish to include this population, then specific ethical approval must be sought to do so, with the appropriate justification.
We will exclude this group from TUS studies until scientific reports show similar absence of effects in this group compared to healthy participants.

3.2 Children

There have been a large number of studies that have been conducted using TMS in the paediatric population. In more than 1100 children (controls and neurologically impaired) there have been no reports of adverse effects (Frye et al., 2008). However, from a neuroscience perspective, the developing brain is physiologically and pharmacologically different from the adult brain.

Safety strategy
Using a similar risk/benefit analysis to that described above, the same general rule applies. Therefore, participants under the age of 16 will be excluded from participation and the inclusion would be predicated upon a specific ethics approval sought with appropriate justification.
For TUS studies, we will exclude participants under the age of 18.
Add a note – before people decide to do an Exp

3.3 Existing Medical Conditions

The activation of a neural population in a stimulated volume is generally predictable in a healthy control population and is dependent upon the brain regions stimulated and the intensity of

the stimulation (see above). However, the extent to which neural activation will occur is less predictable in populations with neurological disorders. In particular, in hyper-excitability disorders such as epilepsy and migraine the activation threshold for the neural population are potentially lower than those in healthy control participants. This brings an increased risk of seizure induction. However, it is worth noting that in an exploratory study of TMS risk in epilepsy, researchers were unable to elicit either seizure or epileptiform discharges in an EEG, in the eight epilepsy patients they tested (Dhuna et al., 1991).
The unpredictable nature of neuronal reorganisation following brain insult, brings an increased risk of the formation of an epileptogenic focus. This is true for patients with conditions of focal or generalized encephalopathy, such as tumor, stroke, meningitis and encephalitis or following severe head trauma (Rosa et al., 2004).

Safety strategy

Screening forms will be used to determine whether participants have any pre-existing medical conditions. In the core activities of the NeMo or the NIBS lab, participants that have suffered brain injury as a result of the following conditions will be excluded from participation in either TMS, tDCS/tACS or TUS studies:

- epilepsy
- tumor
- stroke,
- meningitis
- encephalitis
- severe head trauma

While there is a low-level risk of inducing seizure when the parameters for stimulation safety are used, additional measures will be taken to minimise the risks associated with seizure induction. Individuals with epilepsy or first-degree relatives with idiopathic (non-acquired) epilepsy will be excluded.

3.4 Medications and other drugs

The predictability of the excitatory effects of rTMS are reduced by the introduction of various medications and other drugs. Participants using drugs that lower the convulsive threshold of neuronal populations, or are directly pro-convulsive, incur an increased risk of inducing a seizure using rTMS. Medications such as the tricyclic antidepressants and other antipsychotic medications pose such a risk. In addition, the change in seizure threshold associated with heavy alcohol consumption, is a particularly important consideration for recruitment (Rosa et al., 2004).

With high intensity protocols and the use of contrast agents (microbubbles), ultrasound can transiently open the blood-brain barrier (BBB) by impacting on the permeability of the BBB. As a result, it is possible to deliver drugs in very specific brain areas. Without intervention, the BBB prevents the brain uptake to most pharmacological drugs which have molecular weights and forms that prevent them from crossing the BBB. The ultrasound protocols which open the BBB are very different than the ones used for TUS and it is important to note that the permeability of the BBB is NOT altered with TUS.

Safety strategy

The extent to which medication poses a risk for rTMS studies has not been fully explored. However, the principal concern is the use of pro-convulsive drugs, drugs (or combinations of drugs) that lower seizure threshold or withdrawal from drugs that incurs a lowering of seizure threshold (i.e. anti-convulsant withdrawal).

The potential risks associated with particular drugs can be subdivided into three categories:

Category 1:
Drugs that present a **strong potential hazard** for application of rTMS.

Imipramine
Amitriptyline
Doxepine
Nortriptyline
Maprotiline
Chlorpromazine
Clozapine
Foscarnet
Ganciclovir
Ritonavir
Amphetamines
Cocaine
MDMA
Ecstasy
phencyclidine (PCP)
Ketamine
gamma-hydroxybutyrate (GHB)
Theophylline

Category 2: Drugs that present a **relative hazard** for application of rTMS:

Mianserin
Fluoxetine
Fluvoxamine
Paroxetine
Sertraline
Citalopram
Reboxetine
Ampicillin
Cephalosporins
Metronidazole
Isoniazid
Levofloxacin
Cyclosporine
Chlorambucil

Venlafaxine	Vincristine
Duloxetine	Methotrexate
Bupropion	cytosine arabinoside
Mirtazapine	BCNU
fluphenazine	Lithium
Pimozide	Anticholinergics
Haloperidol	Antihistamines
Olanzapine	Risperidone
Quetiapine	Chloroquine
Aripiprazole	Mefloquine
Ziprasidone	Imipenem
Penicillin	Sympathomimetics

Category 3: Drugs that pose a withdrawal risk:
Barbiturates
Benzodiazepines
Meprobamate
Chloral hydrate.

In line with the safety guidelines, participants taking or having recently withdrawn from drugs in categories 1 and 2 and 3 will be excluded from participation in general studies with rTMS. If patient groups, that might be taking the medications listed, are to be scanned then specific ethical approval (possibly to include NHS ethics) must be sought for this inclusion and the appropriate safety procedures and/or medical support provided.

For TUS, out of an abundance of caution, and to eliminate the potential risk that some drugs or medications (for example antibiotics) taken while participants are undertaking TUS treatments could cross the BBB, we will exclude participants that are taking any medications during the experiment. It is important to reiterate that **TUS protocols do not open BBB** and this measure is taken only out of an abundance of caution.

In addition, participants will also be screened for alcohol use and required to abstain from alcohol for 24 hours before their stimulation.

3.5 Seizure

3.5.1 TMS

Seizure induction is the most sever acute adverse risk for TMS. Several cases of seizure induction have been reported to date. Seizures are cause by the hypersynchronous discharge of large groups of neurons in the grey matter, which is the result of hyperexcitability in the brain networks. Using rTMS, it is possible to influence the firing rate of groups of neurons, resulting in the generation of a seizure. The majority of cases reported occurred prior to the publication of defined of safety guidelines by (Wassermann, 1998). A recent systematic review identified 16

cases in which seizure has occurred under experimental conditions (Rossi et al. 2009). Seven of these cases were prior to the 1998 safety guidelines, five of the remaining cases used stimulation protocols that were outside of the 1998 guidelines and the remaining four cases were as follows:

1. A patient receiving rTMS as treatment for major depression. An episode occurred following additional rTMS (110% of motor threshold (MT), 20Hz train for 5 seconds). A brief loss of conciousness, indicative of syncope rather than seizure (Conca et al., 2000).
2. A participant using fluoxetine (a pro-cunvulsant medication) experienced a seizure following rTMS (100% MT, 20Hz for 2 seconds) (Bernabeu et al., 2004).
3. A patient with chronic pain experienced a tonic-clonic seizure following rTMS (100%MT, 10Hz for 10 seconds) (Rosa et al., 2004).
4. A patient with major depression, suffering from sleep deprivation, experienced a generalised tonic-clonic seizure during treatment for depression (110%MT, 15Hz for 10 seconds).

In summary, these cases highlight a number of additional risk factors that should be considered in the design of a TMS experiment:

Safety strategy

The risk of seizure is greatly increased in specific patients with neurological disorders or lesions as highlighted previously. These groups will be excluded from participation. In addition to this, the risk to the general participant group will be minimised by strict adherence to safety guidelines as discussed I the following section.

3.5.2 tES

As discussed in the comparison of TMS and tES mechanisms (section 1.3), the important difference with tES (tDCS and tACS) is that it does not elicit neuronal firing at the current applied (1-2mA), but instead alters the membrane potential of the neurons in that region (Nitsche and Paulus, 2000). Because the induction of seizure occurs as a result of the increase in large-scale neuronal firing, it is greatly reduced in tES studies. Indeed, in over 200 published studies, with hundreds of participants undergoing thousands of tDCS sessions, there have been no reports of serious adverse events with current strengths up to 2mA and continuous application of current up to 30-minutes (Kessler et al., 2012).

Safety strategy

While there have been no reports of seizure induction with tDCS, likely due to the absence of induced neuronal firing, it is important to consider the possibility of seizure induction by changing membrane potentials in susceptible individuals. Specifically, if a participant is predisposed to seizure activity because they may be epileptic, or have their seizure threshold reduced by medication or illness, then there is an increased risk posed by tES. Therefore, the same screening rules used for TMS will apply to tES. In addition, as standard, the protocols will not exceed those reported in the literature to be safe.

3.5.2 TUS

As discussed in the introduction, TUS has a very high spatial accuracy with a region of 90%-maximum intensity that does not exceed few millimeters shaped in an ellipse form. In addition, there is variability in neuronal responses to TUS. This precludes the possibility of large-scale neuronal firing compared to TMS where the spatial distribution extends to several centimeters in some directions. In addition, there has been no report of seizure in more than 10 human studies and more than 30 animal studies (Pasquinelli et al., 2019; Legon, 2020).

Safety strategy

We will apply the same screening rules used for TMS and tES. In addition, as standard, the protocols will not exceed those reported in the literature to be safe.

4 Stimulation parameters

4.1 Repetitive Frequency Stimulation

The intensity of stimulation in each participant is directly related to the volume of the brain that is stimulated and therefore the population of neurons that are activated. Individual differences in participant anatomy, such as skull thickness, results in differences in the volume of stimulation at the same intensity. The effects of stimulation intensity can be measured in the motor system, using single-pulse stimulation of the primary motor cortex (M1) using electromyography (EMG) to obtain the MT measurement. Safety guidelines are typically expressed in terms of percentage of MT.
The frequency of stimulation refers to the rate at which the stimulation is applied. This is expressed as pulses per second (Hz) and typically varies from <1Hz to 25Hz in most TMS experiments. Frequency is not a consideration with tDCS, as the current is continuously applied for the duration of the trial. In tACS experiments, frequencies may be applied over a broader range from >1Hz to >100Hz. In the case of TMS, where each pulse has the potential to generate a neuronal firing, the greater the frequency and the greater the overall intensity of stimulation and the capacity for neuronal excitation; dependant upon the duration of stimulation (see below).
The duration of stimulation is a key factor in determining the overall intensity of the stimulation. When designing a safe study protocol, a combination of intensity, frequency and duration must be considered.

Safety strategy

The safety profile of stimulation parameters has been thoroughly investigated in recent years. The result of this is a series of guidelines, detailing the safe limits of stimulation in terms of intensity (MT), frequency (Hz) and duration (sec). (Table 2).

Inter-train interval (ms)	Stimulus intensity (% of MT)							
	100%		105%	110%			120%	
Part A								
5000	Safe		Safe	Safe			Insufficient data	
1000	Unsafe (EMG spread after 3 trains)		Unsafe[a]	Unsafe (EMG spread after 2 trains)			Unsafe (EMG spread after 2 trains)	
250	Unsafe[a]		Unsafe[a]	Unsafe (EMG spread after 2 trains)			Unsafe (EMG spread after 3 trains)	
Frequency (Hz)	100%		110%		120%		130%	
	Duration (s)/pulses		Duration (s)/pulses		Duration (s)/pulses		Duration (s)/pulses	
Part B								
1	>270	>270	>270	>270	>180	>180	50	50
5	10	50	10	50	10	50	10	50
10	5	50	5	50	3.2	32	2.2	22
20	1.5	30	1.2	24	0.8	16	0.4	8
25	1.0	25	0.7	17	0.3	7	0.2	5

Table 2. Safe stimulation parameters. Part A shows the results of safety tests on the minimum interstimulus (train-train) interval for 10 trains of 20Hz

stimulation. Part B shows the intensity, duration and pulse number that should not be exceeded.

Summary of Table 2

4.1.1 Inter-train interval

The data in table 2 (upper panel) indicate that the known safe limits for the time between trains of stimuli are at a minimum of 5-seconds. While it is unclear whether 4, 3, 2 (or even 1.5) second intervals are safe, it is known that 1-second intervals are not as they elicit spreading activity in the EMG after 3-trains. At 5-second intervals, the safe amplitude is known to be up to 110% of motor threshold, while there is insufficient data above this amplitude.

4.1.2 Duration of stimulation

The data in table 2 (lower panel) indicate the duration of stimulation and number of pulses that are considered safe at intensities from 100-130% motor threshold. This is calculated for each frequency of stimulation for 1-25Hz. For example, at a stimulation intensity of 100% motor threshold, it is considered safe to stimulate at 1Hz for more that 270 seconds (270 pulses) and at 25Hz it is considered safe to stimulate for 1-second (25 pulses). Whereas, at 130% motor threshold, it is considered safe to stimulate at 1Hz for 50 seconds (50 pulses) and at 25Hz for 0.2-seconds (5 pulses).

4.2 Patterned Stimulation

The use of patterned stimulation has developed as an important aspect of TMS protocols. The most prominent use of this approach is the use of theta burst stimulation (TBS) as a human counterpart of long-term depression or potentiation (LTP/LTD). These approaches use specific patterns of stimulation to reinforce or reduce the efficacy of specific connections within a network. There are several approaches that have been suggested for this approach, however a standard protocol has emerged over recent years, which has proven to have a strong safety record. There are three types of TBS, as described more specifically in the next section, but they are illustrated schematically by (Huang et al., 2005) Huang et al. (2005):

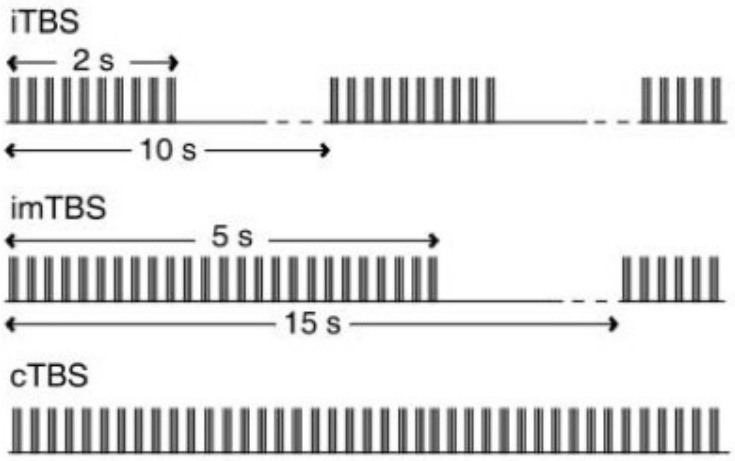

Figure 10. TBS Protocols. Shows the schematic representation of intermittent TBS, intermittent TBS and continuous TBS.

These protocols have been reported in more than 757 participants in more than 50 studies, with only a single incidence of seizure. This incidence occurred when experimenters used a stimulation level of 120% motor threshold, rather than the recommended 80% used in the other studies (Rossi et al., 2009).

4.3 tES

There is a greatly reduced risk of adverse effects in tDCS and tACS (Kessler et al., 2012). However, to minimise this further, the same screening criteria will apply. The standard stimulation protocols used in the NeMo or the NIBS lab will follow those known to have proven safe in previous studies (Kessler et al., 2012):

Stimulation amplitude: will be limited to a maximum of 2mA.

Stimulus Duration: will be limited to a maximum of 30 minutes continuous stimulation.

4.4 TUS

As stated in sections 1.4.1 to 1.4.5, the TUS parameters differ greatly from the ones use in diagnostic ultrasound, high-intensity ultrasound (for ablation studies) or for opening the BBB. In order to create neuromodulation effects, TUS needs to be administered with low intensity and in pulsation mode. The main TUS parameters are detailed in figure 11.

1) At the shortest time scales, the pulses are defined with their associated pulse repetition frequency (PRF) and pulse length (PL)

2) At the middle time scales, the burst duration (BD) includes the burst duty cycle (BDC). The bursts are delivered at a burst repetition frequency (BRF). The time between each burst is defined as the inter-stimulus interval (ISI).
3) At the longest time scales, the total time (TT) of the experiment has an associated total duty cycle (TDC) that refers to the duty cycle over the whole experiment, accounting for the ISI between bursts.

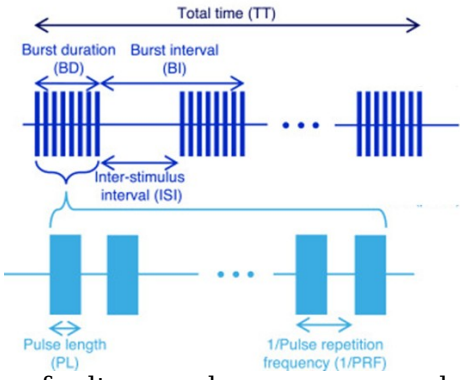

Figure 11. Schematic of ultrasound sequences and associated parameters typically utilized for ultrasonic neuromodulation.

As stated in section 2.3.3, TUS parameters are regulated by FDA, using the following limits. I_{sppa} must not exceed 190 W/cm^2, I_{spta} must not exceed 720 mW/cm^2, and MI cannot exceed a peak negative pressure of 1.9. MI is related to the possibility of cavitation effects and thus is used widely as a safety index. Moreover, we will also follow the IEC 60601 section focused on safety standards for therapeutic equipment, which limits the acoustic intensity at 3 W/cm^2.

4.5 Further Paradigms and Monitoring

All further details of stimulation amplitude, frequency, duration and pulse number for TMS can be derived from table 2. Protocols to be conducted in the NeMo and the NIBS labs will use the above table as initial guidance on the safety limits of the stimulation parameters to be used. The safety guidelines will be monitored continually through alerts from the main journal sources (e.g. Clinical Neurophysiology (Maizey et al., 2013)) and attendance of the annual conference on brain stimulation (Magstim UK).

5 Standard Protocols

5.1 General Safety Protocols

Following the identification of safety standards, discussed in previous sections, the NeMo and the NIBS labs will operate within the recommended safety guidelines as the standard protocol. Below are examples of some initial protocols that will be used for experimental purposes.

5.1.1 Brain Stimulation Location

The location of stimulation for single pulse stimulation will be restricted to cortical regions, in line with the functional implications of the technique and the safety considerations. Therefore, direction of the coil should be to the cortex and avoid stimulation of the brain stem, other deep brain structures or the ocular structures. In order to ensure this is the case, **stimulation must be delivered**:

- Above the level of the inion, identified as the raised bone at the back of the head (figure 12).
- Above the level of the pre-auricular points, identified as the central points of the ears on left and right sides of the head (figure 12).
- Above the level of the supraorbital ridge, identified as the brow-bone ridge above the eyebrows at the front of the head.

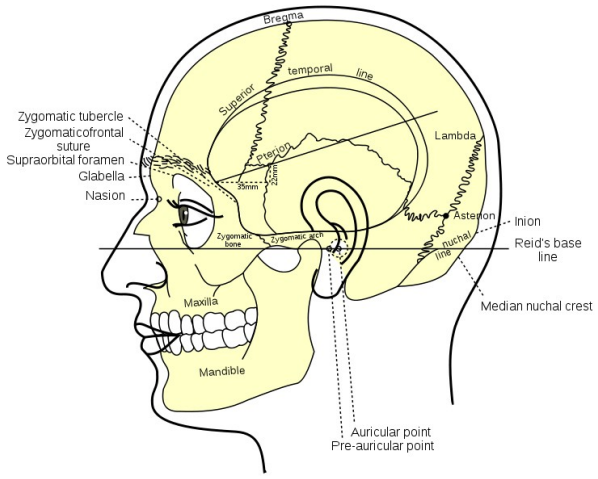

Figure 12. Cranial Landmarks for TMS Stimulation. Image showing the structures of the head to be used to identify acceptable regions for brain stimulation.

5.1.2 Determining Stimulation Thresholds

The basis for all TMS safety guidelines is the use of motor threshold (MT). **It is important to clarify that here we will be referring to the use of active motor threshold as MT,** as this is lower than resting motor threshold. The reason for this is the ability to determine the physiological effect of stimulation intensity can be determined through measurement of the muscle activity using EMG. This involves stimulation of the motor cortex and, therefore, provides a direct representation of the intensity required for normalised stimulation of that area. However, although it is not possible to obtain comparably reliable objective measurements from other regions of the cortex, it can be assumed that to a large degree the factors that influence the relationship between TMS input and EMG output are transferable to other regions.
Therefore, in each experiment, the stimulation level for each participant should be determined by determining the MT using a standard motor cortex stimulation protocol. This is good practice for both experimental design and safety consideration.

5.2 Single Pulse Stimulation

The application of single pulses of TMS, which we will define here as 1-pulse/≥2 seconds (i.e. ≤ 0.5Hz), is considered to be safe for general use across the brain. Therefore, this will be routinely used in experimental paradigms for all areas of cognitive and behavioural research. The guidance for using this approach will be as follows:

5.3 Repetitive Frequency Stimulation

As discussed previously, there are a number of considerations when designing and employing a frequency specific rTMS paradigm. This relies on the interaction of stimulus intensity, frequency, duration or number of pulses and inter-trial interval. For standard protocols the NeMo or the NIBS lab will follow the guidelines described in table 5. In summary, the following parameters will be adhered to:

- Stimulus intensity of 130% MT or below.
- Frequencies 25Hz or below.
- Duration of 270 seconds or below at 1Hz, at 100% MT or below.
- Frequency, %MT, duration to follow the guidance in table 2.

In general, the guidance for comfort will be followed as described previously and experimenters will be asked to pay close attention to their participants for any unexpected signs of adverse effect.

5.4 Patterned Stimulation

In general, the use of patterned stimulation (outside of the guideline in Rossi et al., 2009) will require specific justification, including demonstration of adequate experimental basis and considerations for safety using the guidance provided in this report. For non-standard protocols, the NMGC will convene to consider its support of the request based upon the safety implications presented from the existing literature and using a cost-benefit analysis. The NMGC will work with the applicant to advise on these issues, before referring the applicant for full submission to the ethics committee.
The appendices of the report will be periodically updated to include the details of each project that is approved to commence for reference by the committee. The only existing patterned stimulation that will be included in the initial standard protocol suite, will be theta burst stimulation (TBS), as described below.

5.4.1 Theta Burst Stimulation (TBS)

In line with previous studies, the approved protocol for TBS will be those that have been previously applied as described in the literature. Specifically, continuous TBS (cTBS), intermittent TBS (iTBS) and intermediate TBS (imTBS) protocols described in Huang et al. (2005), will be recognised as a standard protocol for TMS experiments. In summary, all stimulation will be limited to a maximum of 80% active MT. The three TBS methods are as follows:

cTBS: is 3-pulses at 50Hz, repeated every 200ms, for a maximum of 40-seconds. Providing a total of 600 pulses.

iTBS: is 3-pulses at 50Hz, every 200ms, for 2-seconds, repeated every 10-seconds, for 190-seconds. Providing a total of 600 pulses.

imTBS: is 3-pulses at 50Hz, repeated every 200ms, for 5-seconds, repeated every 15-seconds for 110-seconds. Providing a total of 600 pulses.

5.5 Transcranial Ultrasound Stimulation

5.5.1 Transducers

TUS protocols typically involve a single-element transducer but it is possible to couple more than one element (for example to deliver acoustic energy in two different brain regions). Transducers for cortical targeting are usually small (around 30 mm diameter) and

have a resulting similar focal length) which results in a ~3–4mm and ~1–2cm lateral and axial resolutions respectively. In order to reach deeper structures, transducers are larger (around 70 mm diameter) to reach a similar depth.

5.5.2 Neuronavigation

In order to plan and guide TUS neuromodulation, CT and anatomical MRI of the participants' head are used, in a way identical to TMS.

5.5.3 Parameters

The TUS parameters typically used for brain neuromodulation are a frequency (F in table 3) around 250–500 kHz delivered with approximatively a 300–500 ms burst of about 0.5 ms pulses (BD in table 3) at a PRF of about 1 kHz, with pressure amplitudes on the order of 0.1–0.6 mPa in the brain (PA in table 3).

Examples of parameters used in human neuromodulation (a more complete list of human protocols can be found in Blackmore et al 2019, supplementary material):

	F (MHz)	I_{SPTA} (mW/cm²)	I_{SPPA} (mW/cm²)	PA (mPa)	BD (ms)	BI (s)	PL (ms)	PRF (Hz)	BDC (%)	N	MI
Legon et al 2018	0.5	0.16	0.44	0.12	500	8-10	0.36	1000	36	100	x
Legon et al 2018	0.5	2.53	7.03	0.48	500	4	0.36	1000	36	300	0.56
Ai et al 2016	0.5	2.16	6	0.44	500	12-14	0.36	1000	36	90	x
Lee at al 2016	0.27	0.85	1.7	0.24-0.62	300	2.5	1	500	50	50	0.2-1.2
Mueller et al 2014	0.5	2.12	5.9	0.44	500	6	0.36	1000	36	120	x

Table 3. Examples of TUS studies in humans. Tabulated data are extracted for brain ultrasonic neuromodulation studies from (Blackmore et al., 2019).

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A Appendix

A1 Neural Stimulation Governance Committee (NSGC)

The current system for monitoring safety and determining strategy for brain stimulation techniques at Plymouth University is the regular convention of the NSGC to discuss the maintenance and development of the information contained within this report and update as necessary. The NSGC will form a first stage contact for the submission and refinement of brain stimulation projects and ethics submissions.

The role of the NSGC in respect of new project proposals will be to work with the principal investigator or their delegated researcher to ensure safety and advise on the principles of cost-benefit that are central to this report.

In the interests of promoting good practice, the NSGC will not have the authority to decline projects, but will act as an advisor to the prospective researcher on issues of safety and experimental design and will act to ensure that the strategies discussed in this report are not compromised.

The NSGC will consist of a chair, at least two core members and an independent advisor. The current NSGC:

Chair: Stephen Hall

Members: Giorgio Ganis
Matt Roser
Elsa Fouragnan

Advisor: Lennart Verhagen
(assistant Professor Donders Institute Netherlands)

A2 Seizure Information Form

In the unlikely event of seizure, the following guidelines will be included in the training materials and in the lab:

Do

- Make a mental note of the time
- Call for nearby help if possible.
- Protect the person from injury - (remove harmful objects from nearby)
- Cushion their head
- Look for an epilepsy identity card or identity jewellery
- Aid breathing by gently placing them in the recovery position once the seizure has finished (see pictures)
- Stay with the person until recovery is complete
- Be calmly reassuring

Don't...

- Restrain the person’s movements
- Put anything in the person’s mouth
- Try to move them unless they are in danger
- Give them anything to eat or drink until they are fully recovered
- Attempt to bring them round

A3 Emergency Form

NeMo Lab and NIBS lab at BRIC

PROCEDURE IN CASE OF COLLAPSE OR SEIZURE

If a person collapses, becomes unresponsive, or appears to be having a seizure while using the NeMo Lab or NIBS lab at BRIC:

1. **Ease them gently to the floor and make sure their head is supported by a pillow or blanket. Move equipment out of the way.**
2. **Call security and ask them to call an ambulance.**

   Give location as:

A4 Incident Report Form

TMS Incident Report

Date _____ **Time** _____

Severity (Minor, Major) _____
_____

Subject (Gender) _____

Tester(s) _____

Description (Please include the experimental details. Be sure to mention the type of stimulation, the site, and the cumulative amount received. Use additional pages if necessary).

A5 Incident Report Form

TUS Incident Report

Date _____ **Time** _____

Severity (Minor, Major) _____
_____

Subject (Gender) _____

Tester(s) _____

Description (Please include the experimental details. Be sure to mention the type of stimulation, the site, and the cumulative amount received. Use additional pages if necessary).

A6 Participant Report of Symptoms for TUS studies

Subject ID: PI:

Participant Report of Symptoms

Type of Non-Invasive Brain Stimulation: TMS____tFUS_____Other (Describe):_____

Visit Date:		**POST** Time: Investigator:	
How are you feeling overall right now?	Participant		
"Right now, do you feel you have or are.....?"		**Value** 1 absent 2 mild 3 moderate 4 severe	**Relation** 1 unrelated 2 unlikely 3 possible 4 probable 5 definite
Headache			
Unusual feelings on the skin of your head			
Neck pain			
Tingling			
Itchiness			
Sleepiness			
Difficulty paying attention			
Unusual /feelings, attitude, emotions			
Tooth pain			
Change in hearing			
Nausea/Sick to Stomach			
Unusual twitches or movements in muscles			
Dizziness			
Anxious/Worried/Nervous			
Forgetful			
Difficulty with your balance			
Change in movement in your stronger hand			
Abnormal sleep last night			
Seizure within the last 24 hours			
Other:			

A7 Current Projects