

**Title: The causal role of neocortical beta events in human sensory perception**

NCT Number: NCT04062318

Approval Date: 02/24/2021



BROWN

## Brown University Application for Full Board / Expedited IRB Review

**Protocol Title:** The causal role of neocortical beta events in human sensory perception

**Principal Investigator (PI):** Stephanie R. Jones, Ph.D.

**PI Phone number & email address:** [REDACTED]

**Is this an undergraduate student project?**<sup>1</sup> ☐ Yes ☒ No

**If yes, name of undergraduate student:**

**Department:** Neuroscience

**Human Subjects CITI training is complete (PI, student & advisor):** ☒ Yes ☐ No

**Good Clinical Practices (GCP) training is complete (clinical trials only; required for HRPP to release approval):** ☐ Yes ☐ No ☒ N/A

**Are there multiple sites involved with this study?** ☐ Yes ☒ No

- If "yes," review the [Application for IRB Authorization Agreement](#)

### Funding Source(s):

- If there is no external funding for the project, enter "University;" if funded by a specific internal funding mechanism (e.g., Mellon Mays Fellowship, Royce Fellowship, UTRA, OVPR Seed funds, etc.) please specify: P20GM103645 Center for Central Nervous System Function NIGMS COBRE
- If externally funded, the project title and grant/contract # must be provided:

## PART I. HUMAN SUBJECTS RESEARCH SCREENING

**Full Board/Expedited studies must meet the federal definition of "Human Subjects Research." Answer the following questions to determine if your proposed study meets the federal definitions of both "Research" and "Human subjects."**

<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	Is this study a <a href="#">systematic investigation</a> ?
<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	Is the <i>primary design intent</i> of this study to contribute to <a href="#">generalizable knowledge</a> ?
<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	Is the information being obtained <i>about</i> living individuals?
<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	Will you collect information through some type of intervention or interaction? <b>OR</b> Will you have access to <a href="#">individually identifiable information</a> ? <b>OR</b> Will you have access to <a href="#">private information</a> ?

If you answered "no" to any of the above questions, your study does not meet the definition of "Human Subjects Research." You are not required to submit an Application for IRB review to the Brown HRPP.

<sup>1</sup> Most Undergraduate student projects do not require IRB/HRPP review and oversight. Before completing this application, please refer to Brown's [Guidance Regarding Undergraduate Work Involving Human Subjects Research](#).

Before proceeding, be sure to review the revised Common Rule [categories](#) for Exemption to determine if your study meets criteria for Exempt review and the [Application for Exemption](#).

## PART II. RISK ASSESSMENT & EXPEDITED ELIGIBILITY SCREENER

**1. Minimal Risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examination or tests.**

**Using this definition, do you believe this research presents:**

<input type="checkbox"/> No greater than minimal risk (Expedited)	Briefly justify this selection (and proceed to Question 2):
<input checked="" type="checkbox"/> Greater than minimal risk (Full Board)	Briefly justify this selection (and proceed to <a href="#">Part III</a> ): this study will utilize magnetic resonance imaging (MRI), electroencephalography (EEG) and transcranial magnetic stimulation (TMS) of healthy adult participants. Though all of these techniques are used clinically and are considered to be safe, non-painful and non-invasive, they do confer some risk higher than that anticipated to be encountered in ordinary daily life due to exposure to strong magnetic fields (MRI & TMS), and induced electrical fields (TMS).

**2. Below are Research Categories *eligible* for Expedited Review. Select one or more of the categories that are applicable to your proposed research, if any.**

<input type="checkbox"/> Category 1	Clinical studies of drugs and medical devices only when condition (a) or (b) is met (please select one): <input type="checkbox"/> (a) research on drugs for which an IND application is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review); OR <input type="checkbox"/> (b) research on medical devices for which (i) an IDE exemption application is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.
<input type="checkbox"/> Category 2	Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows: <input type="checkbox"/> (a) from healthy, non-pregnant adults who weigh at least 110 pounds. For these participants, the amounts drawn must not exceed 550 ml in an 8-week period and collection may not occur more frequently than 2 times per week; OR <input type="checkbox"/> (b) from other adults and children, considering the age, weight, and health of the participants, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these participants, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8-week period and collection may not occur more frequently than 2 times per week.
<input type="checkbox"/> Category 3	Prospective collection of biological specimens for research purposes by noninvasive means. Examples may include:

	<p>(a) hair and nail clippings in a non-disfiguring manner;</p> <p>(b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction;</p> <p>(c) permanent teeth if routine patient care indicated a need for extraction;</p> <p>(d) excreta and external secretions (including sweat);</p> <p>(e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gum base or wax or by applying a dilute citric solution to the tongue;</p> <p>(f) placenta removal at delivery;</p> <p>(g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor;</p> <p>(h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques;</p> <p>(i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings;</p> <p>(j) sputum collected after saline mist nebulization.</p>
Category 4	<p>Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)</p> <p>Examples may include:</p> <p>(a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy;</p> <p>(b) weighing or testing sensory acuity;</p> <p>(c) magnetic resonance imaging;</p> <p>(d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography;</p> <p>(e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.</p>
<input type="checkbox"/> Category 5	<p>Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis). NOTE: Some research in this category may be Exempt. Review the <a href="#">categories for Exemption</a> before selecting this option.</p>
<input type="checkbox"/> Category 6	<p>Collection of data from voice, video, digital, or image recordings made for research purposes.</p>
<input checked="" type="checkbox"/> Category 7	<p>Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. NOTE: Some research in this category may be Exempt. Review the <a href="#">categories for Exemption</a> before selecting this option.</p>



**1. Introduction and Background.** *In reviewing the protocol, the IRB must consider the rationale for the study and the importance of the knowledge that may reasonably be expected to result.*

Low-frequency brain rhythms in the alpha (8-14) and beta (15-29 Hz) bands are some of the most dominant brain signals that can be measured non-invasively in humans with magneto- and electro-encephalography (MEG/EEG). They are strong predictors of perception and functional performance in a range of tasks, and have been observed to be disrupted in disease states. Yet whether and how these rhythms exert a truly causal influence on cortical function remains unknown, limiting the ability to harness these prominent brain dynamics to improve function with pharmacology or brain stimulation-based interventions. In this proposal, we will combine human EEG, non-invasive brain stimulation (transcranial magnetic stimulation; TMS) and biophysically principled neural modeling to investigate a direct causal relationship between low-frequency brain rhythms and sensory perception, and define novel TMS paradigms that optimally impact perception.

Prior studies in our lab have investigated touch perception using MEG and a tactile detection task in which participants receive a very light (just barely perceptible) tap to the finger, and then report whether or not they felt it. All else equal, participants are less likely to perceive the tap when alpha and/or beta power in primary somatosensory cortex (SI) is high than low, and power shifts across cortical regions with attention. More specifically, alpha/beta power tends to be higher in non-attended, and lower in attended, somatotopic brain representations. It has been suggested that this represents a mechanism for filtering distracting information to facilitate perception (Jones et al J. Neurosci. 2010).

Our lab has also shown that high power *beta* activity is not an ongoing oscillation, but instead emerges as brief “events” (<150ms) in unaveraged data- the appearance of an oscillation is due to the common data processing practice of averaging signals across trials (Sherman et al PNAS 2016). Furthermore, such beta events are intermittent, and the rate and timing of events underlie the previously described attentional and perceptual effects associated with beta power (Shin et al., 2017).

These findings were previously observed across species and recording devices (human MEG and mouse LFP, Shin et al., 2017), but the robustness of this phenomenon in human EEG data remains to be shown. It is also unknown whether the alpha rhythm exerts similar functionally-relevant event-like characteristics.

In this study, we will use EEG and a non-painful tactile detection task (similar to that previously utilized in the lab) to test whether the rate and timing of ongoing rhythmic events in the alpha/beta bands prior to a tactile stimulus (finger tap) causally impact touch perception, and how this relates to attention. We will further develop safe TMS protocols that mimic endogenous low-frequency event patterns, and test whether they temporarily impact perception in a manner similar to low-frequency events. Finally, we will leverage computational neural modeling that has been previously developed in our lab to simulate macro-scale EEG signals, in order to aid in the interpretation of potential neural circuit mechanisms underlying features of our acquired EEG data.

**2. Specific Aims and Study Objectives.** *The IRB must evaluate the objectives of the research in order to determine whether the risks to participants are reasonable in relation to the importance of the knowledge that may be gained.*

Several factors reduce our understanding of low-frequency alpha and beta rhythms, limiting the potential to harness these prominent brain dynamics to modulate function. This includes a lack of knowledge on (a) the temporal signatures of low-frequency rhythmic dynamics in un-averaged M/EEG data, which is often transient rather than a continuous ‘rhythm’, (b) the circuit mechanism(s) generating such rhythmic activity, and (c) how to leverage the functional effects of brain rhythms in a controlled manner.

We will address these gaps by combining EEG, transcranial magnetic stimulation (TMS) and biophysically principled neural modeling to investigate a direct causal relationship between low-frequency alpha/beta rhythms and perception. We will also acquire structural and resting state functional MRI data to allow for accurate TMS targeting (“neuronavigation”), to perform source localization of EEG signals, and to better inform our interpretation of TMS-EEG study findings.

This project has three main aims:

x: 01/21/2019

Aim 1: Use EEG recordings to quantify the relationship between EEG-measured endogenous rhythmic alpha/beta events and perception.

We predict that detection of a tactile stimulus in an attended body location will be *inhibited* when the rate of endogenous low-frequency events is high in a corresponding somatotopic brain region, and *enhanced* when it is high in non-attended somatotopic regions.

Aim 2: Quantify the impact of TMS on EEG signals and perception using MRI-navigated TMS and simultaneous EEG recordings.

TMS is an established technique for causally manipulating human brain function in a safe and non-invasive manner. Several different TMS pulse protocols have been used to “inhibit” perception, including continuous theta-burst stimulation (cTBS) and single pulse TMS (spTMS). However, to date, no protocols have been developed to mimic the expression of endogenous rhythmic activity that also “inhibits” perception. We predict that TMS protocols designed to mimic endogenous beta event patterns will inhibit perception more effectively than standard “inhibitory” TMS protocols. More specifically, we hypothesize that single TMS pulses, or ‘bursts’ of 3 TMS pulses, will inhibit tactile perception in a time-dependent manner, mimicking the EEG and perceptual effects of endogenous beta events.

Aim 3: Determine the circuit mechanisms by which TMS inhibits perception using computational neural modeling.

Our group has developed a unique model to simulate the circuit mechanisms underlying macro-scale EEG/MEG signals. The model has been applied to study the neural origin of beta events (Sherman et al., 2016). When we analyze this dataset, we will apply our model to interpret our acquired EEG data. This will allow us to delineate the impact of TMS at the circuit level, and test hypotheses regarding potential mechanisms by which beta-event patterned TMS may influence perception.



STOP

If your study **ONLY** involves the use of identifiable secondary data / biospecimens, including coded data from which you may be able to ascertain identity, skip to [PART VI](#). Otherwise, please continue.

**3. Materials, Methods and Analysis.** *The study design, methods and procedures must be adequately described in order for the IRB to understand all activities in which human subjects will participate. The IRB must also be able to differentiate those procedures that are performed for research purposes from those that are performed for routine care or evaluation.*

Participants will be asked to take part in (I) a MRI session, and then anywhere between 1-3 subsequent (II) EEG and/or (III and/or IV) TMS-EEG session(s). In this way, an individual participant will be asked to take part in anywhere between 2-4 experimental sessions (MRI + EEG with or without TMS), for a minimum total of 4 hours to a maximum total of 11 hours. Only one EEG session (with or without TMS) will take place on a single day, and participants are invited, but not required, to come back for subsequent sessions. If it is convenient for the participant, they may be allowed to have an MRI session on the same day as a subsequent EEG or EEG-TMS session, but will be required to take at least a one hour break in between.

**I. MRI ~ 1.5 hours**

**II. EEG without TMS ~2.5 hours**

**III. EEG with TMS (primary somatosensory cortex) ~3.5 hours**

x: 01/21/2019

Brown University IRB Original Approval: 02/21/2019

Brown University IRB Amendment Approval: 11/06/2019

Brown University IRB Continuing Review Approval 01/16/2020

Brown University IRB Continuing Review Approval 12/10/2020

Brown University IRB Amendment Approval 02/24/2021

#### IV. EEG TMS (control region) ~3.5 hours

##### MRI

This will be carried out as the first session because participants' MRIs will be used for region of interest targeting ("neuronavigation") during subsequent TMS sessions. All scanning will take place on the 3 Tesla Siemens PRISMA MRI scanner at the Brown University MRI Research Facility (MRF), with a standard head coil. We will book a 1 hour time slot for each participant, in which we plan to carry out T1-weighted anatomical imaging, diffusion-weighted imaging, and resting state functional MRI. Structural scans may be used to aid in subsequent analysis of EEG/TMS-EEG data (e.g. EEG source localization and tractography-informed TMS-induced electrical field modeling), and may help account for individual differences in brain state and anatomy that could impact our TMS-EEG results (e.g. resting state functional connectivity network strength).

During the MRI, participants will be asked to rest quietly and lie still with eyes open or closed (structural, diffusion-weighted imaging), or with eyes open and passively gazing at a cross-hair (resting state functional MRI). If we run short on time during the MRI session (e.g. if we need to repeat scans due to motion artifact), we will prioritize acquisition of a clean, high-quality T1-weighted anatomical scan over the remainder of our protocol, so that we remain within the allotted time slot.

##### Perceptual Behavior Tasks

During the EEG and/or TMS-EEG sessions, participants will be asked to take part in a computerized tactile detection task in which they will receive light, non-nociceptive taps to the finger or foot, similar to prior studies by our group (Jones et al., 2010; Sacchet et al., 2015; Sliva et al., 2018). They will subsequently report detection or non-detection of touch stimuli with a keyboard button press. This will allow us to gauge tactile detection, a measure of somatosensory perception, and the effects of attention on perception.

##### Tactile Stimulation

This device is designed to apply light, brief, non-painful and non-damaging taps to the skin. The participant's hand will rest on a solid plastic frame through which tactile stimuli will be delivered via a plastic contactor (similar to a small plastic screw). Stimuli (single cycle of a 100 Hz sine wave, 10 msec. duration) will be generated by fused multilayer piezoelectric benders, and will be applied to the distal pads of the third digit via a Delrin plastic contactor affixed to a piezoelectric bender (7 mm diameter presented within a 1 cm circular rigid surround). The device will not be glued to the skin. Stimulus onset and intensity will be computer-controlled using customized software.

##### EEG

During the tactile detection task, participants will receive continuous non-invasive monitoring and recording of changing brain electrical potentials via scalp EEG. This will allow us to link perception to neural dynamics. To do so, we will use two 32-channel Brain Vision amplifiers, for a total of 64 channels. We will use either actiCHamp Plus or BrainAmp series amplifiers, with either passive BrainCap TMS or active actiCAP slim/snap electrodes and mesh caps. All of this equipment is specifically designed and marketed (vendor Brain Products) to be safe and compatible with concurrent TMS application.

In order to carry out EEG, we will place the mesh electrode caps on the participant's head. We will then prepare the skin underneath each electrode in order to get a good electrical signal. To do so, we may first clean the skin underneath each electrode with an alcohol swab, as needed. This step is used mainly if the participant's hair is unwashed, or if we are using a passive electrode cap. We will then very gently abrade/exfoliate the skin using either a blunt-tipped needle (active electrode caps), or a cotton-tipped wooden swab and exfoliating gel (passive electrode caps), while applying a small amount of adhesive gel into each metal ring. This process is not painful, and may feel like a light scratching sensation. The gel is similar to the consistency of hair gel and can be washed out with water. We have a single-occupancy bathroom down the hall from our EEG & EEG-TMS testing rooms in which there is a sink and shower for participants to wash their hair after the experiment. We will also provide participants with clean towels and shampoo.

We will request that participants try to stay as still as possible while we are actively recording EEG data to prevent degradation of the signal. We will communicate to the participant when we are in a phase of the experiment when this is necessary, and when they can relax and move in an unrestricted manner.

## TMS

During the TMS-EEG study sessions, participants will receive single or triple pulses of TMS over somatosensory cortex or a control location (parietal, temporal or visual cortex) during the tactile detection task, and concurrent with EEG recording. This will allow us to examine the brain response to TMS with high temporal resolution.

TMS is a method for electromagnetically inducing a weak, transient electric field in the human brain. TMS works by passing a brief, powerful current of electricity through a small coil of wire placed near the head. The pulsing of this current through the coil produces a transient magnetic field directly below the coil. Importantly, this magnetic field harmlessly passes through hair, scalp, and skull and induces a brief, weak electrical current in the brain that transiently depolarizes neurons focally underlying the coil. The change in neural activity for this single pulse is very brief (around 1/10 of a second or less) and occurs at a shallow depth (e.g., approximately 1.5 to 2.0 cm below the scalp), depending on the coil geometry and stimulator output intensity.

Participants in TMS experiments sit in a custom chair. They may be reclined in the chair during stimulation or they may sit upright with their head held unrestrained. A coil is placed on the participant's head in various positions and may be held by an experimenter or by a guidance arm. The positioning of the coil on the head may either be determined using head landmarks or an MRI-guided region-of-interest targeting "neuronavigation" system.

### Neuronavigation

When the neuronavigation system is used, the participant will wear a headband or plastic eyeglasses with an attached position tracker. An additional head-tracking tool will identify the location of specific fiducial landmarks on the head as recorded by an optical position sensor (i.e., a special camera with two lenses) mounted to the wall. The coil position is then tracked relative to a canonical brain, the participant's own anatomical MRI, and/or an overlaid fMRI image, and can be visualized by the neuronavigation computer throughout the stimulation session. In cases where the participant's own brain image is used for localization, an anatomical MRI will have been collected during a prior MRI session. We will inform participants that we must use their neuroimaging data from this previous experiment during the TMS consent process, and will obtain their consent to do so.

Stimulation is triggered either manually by the experimenter or automatically by the experimental script. There is no difference in risk or the functioning of the stimulator with either of these options. When the strong current passes through the coil, there is a small degree of movement of the wire coil within its protective casing. This produces an audible "click" when the coil is pulsed. Participants will be required to wear ear plugs to protect them from exposure to this noise.

### Experimental controls

In order to draw inferences regarding the necessity of a specific region of the brain and/or the timing of a particular type of stimulation for somatosensory perception, we require control conditions that match our experimental conditions in terms of the sensations and parameters related to stimulation, but that are different in the variable of interest (e.g., the locus and/or timing of stimulation). In this study, we will incorporate two different types of controls.

- (1) **Within-session 'no stimulation' trials.** During the TMS-EEG sessions, we will collect trials in which TMS pulses are applied, and trials with no TMS pulses, during the tactile detection task. During all trials, the TMS coil will be held over the participant's head as directed by the neuronavigation system, but on "no stimulation" trials, no trigger will be sent from the task code to the stimulator. In the place of a TMS pulse(s), a noise will be played that sounds like the clicking noises made by the stimulator.
- (2) **Between session region of interest "active" control.** Active stimulation control refers to the active stimulation of a region of the brain that is not hypothesized to be necessary for the cognitive control process under study and/or stimulation with a pulse timing that is hypothesized to not affect the process of interest. As active stimulation control involves active TMS stimulation, it will employ identical procedures and protocols to those described below for experimental stimulation conditions. We ask participants to take part in two different TMS-EEG sessions on different days, separated by at least one week. In one session, we will apply TMS pulses over our region of interest in somatosensory cortex. In a second session, we will apply TMS pulses over a control region of interest.

## Locus of Stimulation

For the experiments in this protocol, we will stimulate focal regions of neocortex mainly in the frontal (motor cortex) and parietal lobes. Specific target regions are those that are hypothesized to support somatosensory perception and will be stimulated in order to test for a change in observed outcome measures. Active stimulation control regions that are not hypothesized to be necessary for a particular aspect of somatosensory perception under study will be selected in order to provide an active stimulation control against which the target stimulation condition can be compared. In cases where the participant's own brain image is used for localization, this will have been collected during a prior MRI session.

## TMS Devices

Several devices are used during a TMS experiment, including stimulators, coils, and navigation devices. Below, we briefly describe each device and its purpose. A subset of these devices would be used for each TMS session depending on the specific stimulation protocol and experiment. We indicate these uses in the descriptions below.

Magstim Super Rapid<sup>2</sup> Plus<sup>1</sup>. This stimulator device is used for delivery of repetitive trains of TMS with pulses at high frequency and intensity. The Super Rapid<sup>2</sup> Plus<sup>1</sup> device can produce rTMS at 10 Hz at 100% power and theta burst stimulation at ~60% power.

Magstim Bistim<sup>2</sup>. The Bistim<sup>2</sup> stimulator system couples two Magstim 2002 stimulators for power output needed to conduct single-pulse, paired-pulse and dual-pulse stimulation protocols. The paired-pulse method delivers two TMS pulses through a single coil at variable (programmable) intervals.

Magstim Double Rapid Air Film Coil: This 70 mm diameter "Figure 8" coil is specially designed for rTMS work. Coils used for rTMS require active cooling mechanisms to prevent coil overheating. This coil is air-cooled.

Magstim D702 coil. This butterfly shaped (Figure 8) coil is designed to deliver high-power single-pulse in a narrower field, to activate or suppress a more focal area than is possible with other flat coils. This coil will be used for most single-pulse and paired-pulse work. It could also be used for dual-pulse.

Magstim 50 mm butterfly coil. This coil is designed to deliver more focal stimuli than the D702 coil, though at lower possible peak powers due to its smaller diameter. Used in projects requiring the most focal stimulation possible and for dual-pulse experiments requiring coil placement in close proximity.

Magstim Double Rapid Air Film SHAM coil. This 'sham' coil will have a form factor identical to the Double Rapid Air Film Coil, but without functionality to deliver TMS. The coil will be used for mock-TMS, an important control procedure particularly for research studies employing blinded design.

Magstim D702 SHAM coil. This 'sham' coil will have a form factor identical to the D702 coil, but without functionality. As with the other sham coil, we will use this non-functional coil for experimental control purposes.

Rogue Research Brainsight Stereotaxic Navigation System. This system is used to precisely position TMS coils for stimulation of specific anatomical targets. The system has continuous feedback and plots the presumed brain location and orientation of the TMS pulse trial-by-trial. Neuronavigation interface with TMS is critical given the inherent limitation of using superficial anatomical landmarks and head measurement for establishing target coordinates.

Rogue Research Brainsight Trigger module. This device interfaces with the brain stimulation equipment to permit acquisition of the estimated stimulation site for each TMS pulse or repetitive bout.

Magstim EMG Interface Module. This module allows for control of TMS pulse delivery and delay of the TMS capacitor recharge from a remote PC. It also provides output triggers e.g. to time-lock TMS pulse delivery with the Brainsight Stereotaxic Navigation System and the actiChamp Plus EEG System.

## TMS Stimulation Protocols

We will use the following stimulation protocols across experiments. Only one protocol will be used for any given experimental session, in addition to motor thresholding (see EMG Procedures). Following the protocol descriptions, a summary of stimulation parameters are provided in Table 1. These parameters include the intensity of stimulator output, expressed as a percent of active motor threshold (% MT; see EMG Procedures), the within-train frequency of stimulation (Hz) (i.e., how often per second pulses are delivered in a continuous train), the number of pulses per train or trial, and the inter-train/trial interval (msec.) (i.e., the minimum time separating two trains of pulses, or trials with single pulses).

As detailed in the “Risks and Benefits, TMS” section, TMS is considered low risk when protocols use stimulation parameters within established international safety norms. Parameters and procedures for all protocols cited here are based upon published international consensus safety guidelines (Rossi et al., 2009). In Figures 1 and 2, we have provided the relevant tables from the international consensus safety guidelines published in (Rossi et al., 2009).

Mkon,

#### *Single pulse TMS to primary motor cortex, somatosensory cortex, or a control region of interest*

Delivery of single TMS pulses (< 1 Hz) over motor cortex will primarily be used to assess cortical excitability. The elicited response in EMG of the fingers, hand, or arm will be recorded (see EMG Procedures). These data are conventionally used to calibrate stimulator output intensity, which is known as “motor thresholding”.

Single TMS pulses to motor cortex, somatosensory cortex, or a control region of interest can also be used to characterize local changes in excitability due to experimental manipulations.

The time between single TMS pulses will be irregular, but they will always be delivered at least 3 seconds apart. See Figure 1 for relevant safety guideline.

#### *Paired pulse TMS to somatosensory cortex or a control region of interest*

Delivery of paired pulses involve delivery of two pulses, whereby a single pulse is administered 5-500 ms prior to another pulse from the same coil over the same brain region or from another coil over a second brain region. Such paired pulse designs are useful for characterizing changes in the interactions of two neural regions. The time between pairs of pulses will be irregular, as they are determined by the timings of specific trial events that may not be spaced at regular intervals. However, these paired-pulse trains will be administered at least 5 secs apart ( $\leq 0.2$ Hz). Paired pulse stimulation has not been found to be associated with any increased risk relative to standard single pulse TMS (Rossi et al., 2009). See Figure 1 for relevant safety guideline.

#### *Tripe pulse TMS to somatosensory cortex or a control region of interest*

In this custom TMS protocol, we will deliver one set of three rapid biphasic TMS pulses (40-60 Hz “triplet”) per trial while the participant is engaged in a tactile detection task (“online”). The inter-pulse interval within a triplet will be  $\geq 15$  msec., and we will present one TMS pulse triplet per trial. We will design the trial structure of our task such that there is at least a 5 second inter-triplet interval (ITI) between trials. A maximum of 900 TMS pulses total (300 trials of 3 pulses per trial) will be presented during this protocol. Pulses will be delivered at  $\leq 90\%$  of active motor threshold.

This protocol is intended to mimic a single set of triplet pulses that, when continuously or intermittently presented, comprise the fundamental units of conventional cTBS. Although no clear international safety consensus guidelines exist for the protocol that we propose, we have conservatively extrapolated protocol parameters from existing studies that have been safely performed, as follows below.

In conventional Theta Burst Stimulation (cTBS) protocols (Huang et al., 2005), similar biphasic triplets of TMS pulses (50 Hz) are presented continuously for 40 seconds, with a 200 msec. ITI. The standard cTBS protocol for which international safety consensus has been reached involves 600 total pulses per session (200 triplets, 80% active motor threshold; See Figure 2 for relevant safety guideline), but 900 pulses have also reportedly been safely performed (Rossi et al., 2009). Therefore, we will not exceed 900 total pulses (300 trials of 3-pulse triplets) in a single session of triple pulse TMS, and will carry out no more than one session per day for an individual participant.

Quadripulse Stimulation (QPS; Hamada and Ugawa, 2010) is another established type of TMS pulse protocol in which 4 monophasic TMS pulses are presented rapidly, with inter-pulse intervals  $\geq 1.5$  msec. (typically ranging

01/21/2019

between 1.5-2.5 msec.). International safety consensus guidelines have been reached for 1440 total pulses (360 trials) of QPS with an inter-pulse interval between 1.5-1250 msec. at 90% of active motor threshold, given the quadripulse trains are delivered  $\geq$  every 5 seconds (Rossi et al., 2009; See Figure 2 for relevant safety guideline). Therefore, our protocol involves an ITI of at least 5 seconds.

**Table I: Parameter ranges for TMS protocols proposed intensities of stimulator output**

Protocol	Intensity (% Active MT)	Frequency	Pulses/trial or train	Inter-train-interval (sec)
Single pulse TMS	$\leq 120$	$\leq 1$ Hz	1	1
Paired pulse TMS	$\leq 100$	$\leq 0.2$ Hz	2	5
Triple pulse TMS	$\leq 80$	3 x 40-60 Hz at 0.2 Hz	3	5

**Figure 1: Relationship of single-pulse and repeated pulse protocols (Single and paired pulse protocols) to rTMS consensus safety guidelines from Table 4 of Rossi et al. (2009). Blue box indicate where on the table single and paired TMS pulse protocol parameters comply.**

**Table 4**

Maximum safe duration (expressed in seconds) of single trains of rTMS. Safety defined as absence of seizure, spread of excitation or afterdischarge of EMG activity. Numbers preceded by > are longest duration tested. Consensus has been reached for this table.

Frequency (Hz)	Intensity (% of MT)				
	90%	100%	110%	120%	130%
1	>1800 <sup>a</sup>	>1800	>1800	>360	>50
5	>10	>10	>10	>10	>10
10	>5	>5	>5	4.2	2.9
20	2.05	2.05	1.6	1.0	0.55
25	1.28	1.28	0.84	0.4	0.24

<sup>a</sup> In Japan, up to 5000 pulses have been applied without safety problems (communication of Y. Ugawa).

**Figure 2: International consensus guideline for TBS protocols in Table 6 from Rossi et al. (2009). Blue box indicates protocol parameters that are relevant to the design of the triple pulse Protocol proposed in this study.**

**Table 6**

Published TBS (biphasic pulses) and QPS (monophasic pulses) protocols on normal subjects. No significant side effects reported, apart vagal reactions after prefrontal cortex stimulation. Consensus reached for this table.

	Pulses in the burst	Total train pulses	Intensity	Stimulation site
"Standard" cTBS (following Huang et al. 2005)	3 at 50 Hz, repeated at 5 Hz	600 (40 s)	80% of active MT	Motor cortex, PFC <sup>c</sup>
Silvanto et al. 2007	8 at 40 Hz, repeated every 1.8 s	200	60% of the maximal stimulator output	Visual cortex
Nyffeler et al. 2006 <sup>a</sup>	3 at 30 Hz, repeated at 10 Hz	200	80% of resting MT	Frontal eye fields
"Standard" iTBS protocols (following Huang et al. 2005)	3 at 50 Hz, repeated at 5 Hz for 2 s	600	80% of active MT	Motor cortex, PFC <sup>c</sup>
QPS <sup>b</sup> (following Hamada et al., 2008)	4 (ISI ranging 1.5 ms–1.25 s), repeated every 5 s	1440	90% of active MT	Motor cortex

<sup>a</sup> Also repeated TBS in the same session (at 5, 15, 60, 75 min).

<sup>b</sup> 2000 maximal total pulse number per day; highest intensity used resting MT (Y. Ugawa, personal communication).

<sup>c</sup> PFC = prefrontal cortex (Grossheinrich et al. 2009).

## EMG & Motor Thresholding

Electromyography (EMG) is used to accurately and precisely measure electrical potentials in the muscles. Recording electrodes are taped/stuck (if they have a sticker backing) to the skin above a muscle of interest following a brief cleaning of the area using an alcohol wipe. An amplifier is used to amplify small, recorded muscle potential signals. This set up can be used to measure the latency and amplitude ( $\mu\text{V}$ ) of Motor Evoked Potentials (MEPs) in the muscles produced by TMS over the contralateral motor cortex.

The quantified amplitudes of MEPs evoked by TMS are conventionally used to determine motor thresholds for calibration of stimulator output strength across different types of TMS protocols. In this study, the proposed TMS protocols will utilize stimulator output strengths measured as a function of active motor thresholds, as indicated in Table I.

To determine an individual participant's active motor threshold (AMT), we will apply single pulses of TMS to primary motor cortex. AMT is defined as the minimum stimulator intensity needed to elicit a  $100\ \mu\text{V}$  or greater EMG response in a target muscle in 50% of pulses (e.g., 5/10) applied to the contralateral primary motor cortex when the target muscle is voluntarily contracted using 10% of maximum voluntary force.

AMT will be determined by initializing the stimulator's output to a proportion of its maximum output that is expected to yield a 50% probability of eliciting an EMG of the criterion intensity ( $50\ \mu\text{V}$  for resting MT, or  $100\ \mu\text{V}$  for active MT). The intensity of stimulation will then be adjusted incrementally to as much as 100% of stimulator output until the AMT is achieved. The TMS pulses used in this procedure will be delivered no faster than 1 pulse every 5 sec (.2 Hz). This slow rate is well within established safety limits (see Figure 1).

If our highest motor threshold (120% active motor threshold) corresponded to 100% stimulator output, the participant's active motor threshold would be  $\sim 83$ . This is highly unlikely in TMS studies without EEG. However, in studies in which the coil is placed further from the scalp due to large active electrodes, motor thresholds increase due to a quick dropoff in magnetic field strength with distance. Therefore, we will cap the maximum motor threshold at 76. If a participant does not have a motor threshold  $\leq 76$ , they will be paid for a full TMS-EEG session, but then excluded from the study and allowed to leave after the motor thresholding procedure.

**THE BLUE TEXT IN THE FOLLOWING SECTIONS IS A GUIDE TO ENSURE ALL RELEVANT INFORMATION IS INCLUDED IN YOUR APPLICATION. YOU MAY DELETE THE BLUE TEXT BEFORE SUBMISSION**

**4. Participant Population.** *In order to approve research, the IRB must determine that the selection of participants is equitable and reasonably related to the purpose and aims of the research. The IRB must also consider whether adequate safeguards are in place to minimize any risks that are unique to vulnerable populations. To make this determination, the IRB must review all methods and materials used to contact and recruit potential participants, including letters, flyers, emails, etc.*

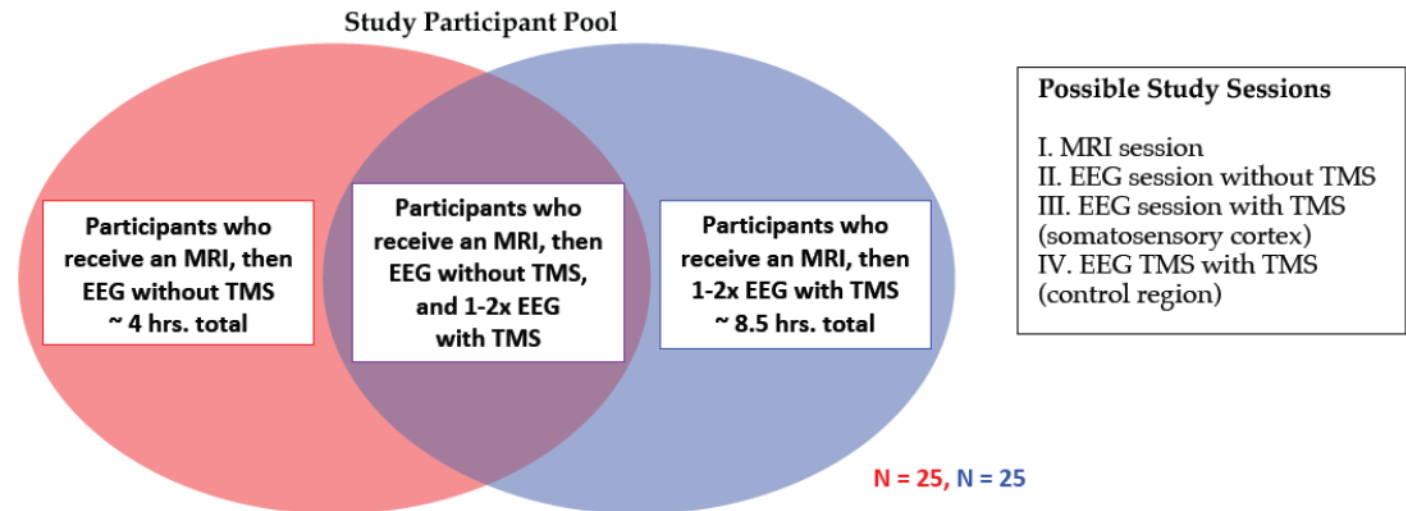
It is necessary to test human participants in this multi-modal study. We will link our EEG and perceptual outcomes to cellular and circuit mechanisms with our unique biophysically principled model of human somatosensory cortex (SI). Additionally, due to the complexity and highly folded nature of the human brain, TMS effects may not directly translate to other species; indeed, one goal of this proposed work is to understand the effects of TMS localized specifically to human SI in order to inform development of therapeutic TMS protocols for clinical human use. Finally, due to the relative size of the human brain in comparison with the TMS coil, TMS is capable of having a more localized and thus interpretable impact on somatosensory processing than if we were to use a smaller animal model.

This project encompasses two separate studies; one in which EEG data is collected concurrent with TMS, and one in which no stimulation is given. Both studies incorporate the tactile detection task previously described, and require an MRI. We would like to recruit 25 participants for each of the two studies, and participants may take part in only one or both studies if they meet the inclusion criteria described. An MRI is needed only once, and the same MRI can be used for both studies. For this reason, the individual visits required for each of the two studies are hereafter all described as "sessions" in order to be less confusing for the participant. Selection of participants for either of the two studies will simply depend on which experiments we are ready to begin/ focus on analyzing when participants express interest. After

v. 01/21/2019

participants take part in an EEG session (with or without TMS), we will let them know that they may be able to participate in additional sessions, and ask if they are interested in returning for the other study.

We plan to recruit 25 healthy adults for experimental sessions consisting of EEG with TMS (sessions I, III and IV), and 25 individuals without TMS (sessions I & II). All recruited participants (including EEG with and without TMS) will take part in an MRI session once (session I) because the MRI data is required for analysis of EEG data, and for acquisition of TMS data. See illustration below.



Upon initial screening, we will let participants know whether they will take part in an EEG session with or without TMS, and that they may subsequently be invited to come back for up to two additional EEG sessions with or without TMS. Our goal is to acquire 25 datasets each of EEG data with and without TMS, respectively.

We plan to recruit healthy adult human participants (18-65 years old) to take part in this study from the Brown University community and greater Providence, RI, area. Participants of any gender, race, ethnicity, religion, sexual preference, residence or family composition will be included. All efforts will be made to include minorities and women in the studies, at the appropriate proportions for the local area. Recruitment will be initiated in response to an e-mail contact from the participant regarding an advertisement. Advertisements may be posted as flyers (see attached), or circulated electronically in e-mail digests and online. We will not initiate contact with students, but will wait for them to approach us for information about the studies.

#### Inclusion criteria

- 1) Ability to provide informed consent/ assent
- 2) Age: 18-65 years
- 3) English fluency: participants must be able to understand screening questionnaires and task instructions spoken/ written in English.
- 4) Right handed: to reduce heterogeneity related to hand dominance, since our task involves touch perception on the hand, and examination of neural correlates in lateralized brain regions.

#### Exclusion criteria

Participants will be screened to exclude individuals with co-occurring neurological or medical conditions that might confound the results. We will also exclude subjects for which TMS or MRI might result in increased risk of side effects or complications:

- 1) History of fainting spells of unknown or undetermined etiology that might constitute seizures
- 2) History of seizures, diagnosis of epilepsy, or immediate (1st degree relative) family history epilepsy
- 3) Any progressive (e.g., neurodegenerative) neurological disorder
- 4) Chronic medical conditions that may cause a medical emergency in case of a provoked seizure (cardiac malformation, cardiac dysrhythmia, asthma, etc.)
- 5) Metal implants (excluding dental fillings)
- 6) Pacemaker
- 7) Implanted medication pump or cochlear implant

v. 01/21/2019

- 8) Vagal nerve stimulator
- 9) Deep brain stimulator
- 10) TENS unit (unless removed completely for the study)
- 11) Ventriculo-peritoneal shunt
- 12) Signs of increased intracranial pressure
- 13) Intracranial lesion
- 14) History of head injury resulting in prolonged loss of consciousness
- 15) Pregnancy
- 16) Participants who have received prior TMS for medical treatment purposes.
- 17) Intellectual Disability or autism spectrum disorder (ASD)
- 18) Active psychosis, diagnosis of unipolar depression or bipolar disorder, active severe substance use disorders (within the last month), or active suicidal intent or ideations.
- 19) Conditions that may result in the inability to effectively carry out the tactile detection task, including loss of feeling, neuropathy or nerve damage in the hands or feet, chronic pain or fibromyalgia, and pain due to cancer, infection or arthritis.
- 20) If the participant is actively taking any of the medications that increase risk from TMS as indicated below, or if they have ingested any alcohol or any other drugs of abuse (see <https://www.drugabuse.gov/drugs-abuse>) on the day of the study session (prior to the session), they will be subject to exclusion from this study.

During the recruitment/screening process, participants will be asked to refrain from alcohol or any other drugs of abuse (see <https://www.drugabuse.gov/drugs-abuse>) on the day of the study session (prior to the study session). They will be told that a reasonable/normal amount of caffeine and/or nicotine is allowed on the day of the study session, however they will be asked to refrain from these substances 3 hours prior to any EEG (with or without TMS) study session. Participants will be encouraged to try to follow their normal routine as closely as possible on the day of the study session.

Please refer to the 'Jones Lab Initial Contact and Screening Form', the 'Jones Lab Participant Information and Secondary Screening Form', and the 'Brown University MRF Magnetic Resonance (MR) Procedure Screening Form for Research Subjects'.

### List of contraindicated drugs

As documented in Rossi et al. (2009), taking one the following drugs may lower seizure thresholds. Note, however, that this is not an exhaustive list. Moreover, it is a list that may be out of date. Thus, any medication being taken by a participant will be cross-referenced against an updated list maintained on <https://www.epilepsy.com/learn/professionals/resource-library/tables/drugs-may-lower-seizure-threshold> AND reviewed by a TMS trained physician [REDACTED] to determine its potential to alter risk for seizure with TMS.

This list of drugs is current as of the time of the writing of the protocol. It is only stated that it may be out of date because new drugs are constantly developed and for that reason we will rely primarily on the judgement of the medical doctor and not on this list.

Imipramine  
 Amitriptyline  
 Doxepine  
 Nortriptyline  
 Maprotiline  
 Chlorpromazine  
 Clozapine  
 Foscarnet  
 Ganciclovir  
 Ritonavir  
 Amphetamines  
 Cocaine  
 MDMA (ecstasy)  
 phencyclidine (PCP, angel's dust)  
 ketamine  
 gamma-hydroxybutyrate (GHB)

v. 01/21/2019

alcohol  
theophylline  
mianserin  
fluoxetine  
fluvoxamine  
paroxetine  
sertraline  
citalopram  
reboxetine  
venlafaxine  
duloxetine  
bupropion  
mirtazapine  
fluphenazine  
pimozide  
haloperidol  
olanzapine  
quetiapine  
aripiprazole  
ziprasidone  
risperidone  
chloroquine  
mefloquine  
imipenem  
penicillin  
ampicillin  
cephalosporins  
metronidazole  
isoniazid  
levofloxacin  
cyclosporine  
chlorambucil  
vincristine  
methotrexate  
cytosine arabinoside  
BCNU  
Lithium  
Anticholinergics  
Antihistamines  
Sympathomimetic

## 5. Recruitment Methods

Recruitment will be initiated in response to an e-mail contact from the participant regarding an advertisement. Advertisements may be posted as flyers, placed on tables, in community newspapers, e-mail digests, and on-line. See attached recruitment document. We will not initiate contact with students, but will wait for them to approach us for information about the studies.

The researcher conducting the recruitment and screening will be knowledgeable about the methods used (behavior, MRI, EEG, and TMS) and will be able to answer any specific questions that the participant may have regarding the risks or procedures associated with the methodology. Safety screening will closely follow published safety guidelines for TMS (detailed in Rotenberg et al., 2014), MRI and EEG. During each experimental session, the researcher will remind the participant that this study is for research purposes only, and not intended to be a clinical intervention or treatment in any way. The researcher will also remind the participant that all study results will be analyzed at the group level, and that individualized study results other than a copy of the participant's structural MRI will not be available.

v. 01/21/2019

Participants will be pre-screened by phone or in-person interview for neurological, psychiatric, or medical contraindications, which may prevent them from participating in the TMS or MRI portions of this experiment. Either [REDACTED] will carry out the pre-screening process using the Jones Lab Initial Contact & Screening Form (see attached). During pre-screening, the researcher will also describe the experimental methods utilized in this study so that the potential participant can make an initial informed decision about their interest in participating. Women will specifically be asked to indicate if there is any likelihood of pregnancy; this will be an additional exclusion criterion since the risks of TMS and MRI to the fetus are unknown. Additionally, we will screen participants for medications that increase risk from TMS. The researcher will discuss any questionable potential exclusionary criteria with one of our collaborating Psychiatrists, [REDACTED] before scheduling the experimental research session.

On the day of the MRI, participants will also be required to fill out the Magnetic Resonance Facility (MRF) Procedure Screening Form (see attached), which will be reviewed by the researcher and MRI technician, as required by Brown University.

On the day of a EEG and/or EEG-TMS session, participants will receive a second follow-up screening questionnaire to fill out (see Jones Lab Patient Information & Secondary Screening Form). This questionnaire is intended to “double-check” for any TMS-exclusionary criteria, particularly any medications or other medical conditions that have changed in the time since the initial phone screening and experimental session, and also to collect valuable demographic and other information pertinent to study design and interpretation. [REDACTED] will review the screening questionnaire before the study session begins.

After taking part in one of our experimental sessions, participants can indicate whether or not they wish to be re-contacted by our lab to take part in additional sessions.

## 6. Compensation / Reimbursement

Participants will be paid in cash at the end of an experimental session, with a total amount per study visit as follows:

- I. MRI session ~ 1.5 hours, \$25 total
- II. EEG session without TMS ~2.5 hours, \$40 total
- III. EEG session with TMS (somatosensory cortex) ~3.5 hours, \$60 total
- IV. EEG TMS with TMS (control region) ~3.5 hours, \$60 total

Participants will be scheduled for the time allotted above, but if the session runs over we will pay them an additional \$15/hour. This overtime is not expected to occur often, and highly unlikely to exceed one hour in total. We do not anticipate that there will be any additional costs to the participant, as we will be recruiting from the local Providence, RI area.

If a participant decides to stop the study or withdraw for any reason before completing the study procedure during a study session, they will still be compensated \$15/hour for their time, rounded up to the nearest hour. For example, if we begin consenting a participant and realize within an hour of arrival that they cannot or will not participate in the study, they will be paid \$15 total for their time.

If the investigator decides to discontinue, the participant will be told the reason why and how they will be compensated. The researcher will offer to further explain or answer any additional questions the participant asks.

**7. Potential Research Risks / Discomforts to Participants.** *In order to approve the research, the IRB must consider the risks posed to participants by the research and any efforts to mitigate those risks. The IRB needs to determine that the risks have been both minimized and are reasonable in relation to the anticipated benefits to participants, as well as to the importance of the knowledge that may be gained. The IRB will also consider whether the informed consent process provides potential participants with an accurate and fair description of the risks or discomforts.*

All members of the research staff will undergo training in appropriate usage, safety, application, and maintenance of research equipment. This includes tactile stimulation, TMS, and EEG. [REDACTED] completed technical and safety training at [REDACTED].

[REDACTED]. She also has extensive experience carrying out MRI studies prior to attending Brown University, and will take part in MRI safety training at the Brown University MRF prior to scheduling any participants for an MRI session of the study. [REDACTED] will be present at all study sessions, along with at least one additional researcher. [REDACTED] have also both received extensive training in the responsible conduct of research, including training from Brown University and CITI training.

There is no deception in these experiments. But, to prevent introducing bias into the results, participants will not be informed of the specific hypotheses or experimental conditions until after the experiment is complete, at which point participants will be fully debriefed. We do not anticipate any physical, psychological, social, legal, or other risks from participation in the cognitive tasks themselves, apart from the potential for boredom and/or mild fatigue.

The potential for loss of electronic and paper records of personal information used for screening may place the participant at low risk for loss of privacy. To reduce the risk of loss of private information, participant identifiable information will be stored separately from individual data and any screening conversations will take place in private. All electronic records will be maintained on password protected file servers in a locked office, further protected by firewalls and other security procedures. Paper records will be maintained in locked file cabinets in locked offices.

## MRI

There are no known significant risks associated with participation in MRI at the levels of magnetic field proposed here, beyond those due to the effect of a magnetic field on an implanted metal fragment or medical device. Hence, all participants are extensively screened for implanted metal. Persons at primary or secondary risk based on an implanted object or medical device will be excluded according to MRF operating procedures. Moreover, no personnel are permitted in the scanner room with any metal on their person. As such, we do not anticipate any significant risk from the application of these procedures. In rare cases, a participant will become anxious because of lying in an enclosed space. We will exclude participants who report a history of anxiety in enclosed spaces, and we will terminate the session of a participant who expresses anxiety about lying in the bore.

All participants will be able to stop the session at any time by squeezing a ball held in one hand. The ball activates a buzzer in the control room. There is also an intercom voice link with the control room that allows verbal communication between participant and experimenters.

## Tactile Stimulation

The design of this stimulator has been used in multiple prior studies without causing injury to the skin (Jones et al.; Sliva et al., 2018). In past experiments, the sensation has been well tolerated and participants have reported that it is not uncomfortable.

Piezoelectric devices can only provide small forces, so even if the device were to malfunction, tissue damage is highly unlikely. The design of the stimulator also inherently limits the amount of pressure that can be applied. Reasonable safe ranges for maximum pressure applied to the skin are known and will be followed conservatively. Additionally, participants will be monitored continuously by a member of the trained research staff while the stimulator is operating, so that the experiment can be aborted if the participant experiences any discomfort or a device malfunction.

Although constant exposure from the device for long periods of time (upwards of 2+ hours) may cause tenderness or a slight scratching to the area of contact, we anticipate participants being exposed for no longer than 1 hour per session. Furthermore, the participant is free to stop the testing at any time if any discomfort.

## EEG

EEG is a safe and painless technique that is routinely used in clinical medicine. The amount of electricity is minimal and there is no risk of electric shock or discharge. The electrode, the cables, and the computer will be tested by biomedical engineers who will certify their safety. Though it is commonly regarded to be a safe technique, there is a possibility participants may experience side effects or discomfort:

(1) EEG may cause minor skin irritation from the use of electrodes, a mild electrolyte gel, and/or adhesive disc electrodes applied to the mastoid bone behind the ear or on the nose. Scraping of the scalp may occur when applying conductive electrode gel scraping of the scalp, which might also add to any discomfort or redness.

(2) Participants may also experience discomfort as a result of sitting still and minimizing self-adjustments during study sessions.

(3) They may also experience discomfort from having the aforementioned electrolyte gel in their hair; however, it is water-soluble and easily rinsed out of one's hair.

During usage of EEG equipment, a member of the trained research staff will continually monitor participants to ensure safety. Furthermore, prior to each trial the electrode cap will be thoroughly cleaned and disinfected to eliminate any transfer of biological debris or contaminants from previous participants. Participants are free to stop the experiment at any time if they no longer desire to continue.

The EEG device will be battery-powered or otherwise electrically isolated from building current.

## TMS

We note that as this protocol covers basic research and does not confer a direct benefit for participants in the experimental condition, standard random assignment is appropriate for any between-participant design. Following participation, we will fully debrief participants about the use of control stimulation.

TMS is low risk given that the stimulation parameters being used are within established safety norms), and we will only enroll healthy participants without contraindication for TMS. In what follows, we detail the specific risks associated with this protocol and the steps we will take to protect against risk beyond those already described in relation to the consent process:

(1) Heating, induced voltages, and magnetic field effects: The action of the magnetic field on any implanted or worn metal in, on, or around the head poses a significant risk. Magnetic fields can move or dislodge metal, induce current in conductive metals, cause heating around metal components, and/or affect the operation of any metal device. Thus, it is crucial to screen participants for any irremovable metal in or around the head.

(2) Hearing changes: Movement of the TMS coil within its casing when current is passed through it produces an audible "click". Though this click is often not perceived as loud due to the stapedial reflex, it can nevertheless reach 140 dB or more of sound pressure. This exceeds OSHA sound level limits and could produce changes in hearing levels if exposed repeatedly. Thus, we will require all participants to wear earplugs.

(3) Induced seizure: Though exceedingly rare even in patients with epilepsy, induction of a "generalized" seizure is the most severe adverse event associated with TMS. A seizure is an episode of excessive brain activity and stiff muscle activity (often referred to as a "convulsion" or "fit"). Seizure risk increases at high stimulator output intensities, at high frequencies of stimulation, with multiple repeated trains of stimulation, with long durations of stimulation, with short inter-train-intervals, and when stimulating participants with reduced seizure thresholds. However, the risk of seizure induction is minimal to negligible if TMS parameters are kept within the prescribed consensus safety parameters (Rossi et al., 2009), and participants are carefully screened for seizure risk. All the TMS protocols proposed here are will be within prescribed safety limits, and a health screening form will include questions to identify participants with potential seizure risk.

(4) TMS application site (scalp) discomfort/headache. The stimulation itself is felt as a tapping sensation on the scalp. The tapping induced by rTMS at high stimulator output intensity can feel sharper and even painful. In addition to a tapping or percussion sensation on the head, muscles and peripheral nerves in the head and face react to TMS with sensations such as twitching of superficial muscle groups.

As described above, acute, severe adverse events during the course of the TMS experiment could include things like superficial burns of participant's skin from TMS coil heating or induction of a generalized "seizure". Other adverse events such as fainting, severe headache, nonspecific stress reaction are possible with TMS and also with other types of brain research. Though our protocol and procedures minimize the risk of these adverse events occurring, all research personnel will be trained to observe the signs of an adverse event, terminate study procedures, and call Brown's Emergency Response System, if it appears a participant is experiencing an adverse event.

## Procedures in the case of an adverse event

As described above, acute, severe adverse events during the course of the TMS experiment could include things like superficial burns of participant's skin from heating of the TMS coil or EEG electrodes, or induction of a generalized "seizure". Other adverse events such as fainting, severe headache, and nonspecific stress reaction are also possible with TMS and other types of brain research.

Though our protocol and procedures minimize the risk of these adverse events occurring, all research personnel will be trained to observe the signs of an adverse event and take the appropriate steps to alleviate any distress a participant may be feeling. For example, the researcher will terminate study procedures and call Brown's Emergency Response System (Brown EMS) if it appears that a participant is experiencing a severe adverse event such as a seizure. The Brown University EMS is a blended volunteer/paid service licensed by the State of RI to provide all levels of pre-hospital care to the Brown community. They provide Basic and Advanced Life Support (BLS and ALS) care and transport 24 hours a day year round except during brief interruptions for periodic maintenance. Brown EMS is staffed by a corps of student volunteers who are licensed RI EMTs and who are assisted by a staff of student and non-student ALS Providers who oversee care when needed.

Research personnel will also be trained to "check in" with study participants throughout study sessions, so that participants feel comfortable communicating any distress they may be feeling to the researcher. Researchers will additionally specifically ask participants about their well-being after the study session is over, and inquire if any of the aspects of the experiment (e.g. sound of TMS clicks) negatively impacted them in any way.

Any adverse event that comes to the researcher's attention either by observation or communication with the participant will be documented and communicated to the IRB.

Two researchers will always be present at any given TMS session in case of an emergency so that one researcher can stay with the participant, while the other researcher seeks help from Brown EMS and the study Principal Investigator.

### **Safety plan for seizures**

The following plan has been adapted from the Center for Disease Control, ([http://www.cdc.gov/epilepsy/basics/first\\_aid.htm](http://www.cdc.gov/epilepsy/basics/first_aid.htm))

1. Keep calm and reassure other people who may be nearby.
2. Immediately end on-going experiment, remove any equipment involved (tACS, tactile stimulator, EEG), and remove any other hard or sharp materials in the area near the participant.
3. Call Brown EMS at 401-863-4111.
4. Make note of when seizure begins.
5. Recline participant in testing chair, if at all possible, making sure arm rests are in place so the participant does not fall out of the chair.
6. If possible, turn the participant gently on their side.
7. Remove eyeglasses and loosen ties or anything around the neck that may make breathing difficult.
8. Stay with the participant until EMS arrives.
9. Be friendly and reassuring as consciousness returns.
10. Contact the Principal Investigator as soon as possible.

### **DO NOT ATTEMPT THE FOLLOWING:**

- 1) **Do not** put anything in the person's mouth. Do not attempt to hold or touch the patient's tongue, face, or head during a seizure.
- 2) **Do not** hold the person down or try to stop his movements.
- 3) **Do not** attempt artificial respiration.
- 4) **Do not** offer the person water or food until fully alert.
- 5) **Do not** administer any medications to the person.
- 6) **Do not** permit the person to leave the research area or go home without evaluation by a medical professional.

The safety plan detailed above will be posted in the TMS suite, both in the testing room and in the outer control room (see attached Safety Plan Poster). In addition, the telephone number for Brown EMS (401- 863-4111) will be posted clearly above the telephones available in the TMS suite.

**8. Potential Benefits of the Research. NOTE: Compensation for participation is not a benefit and should not be included in this section.** *In order to approve this research, the IRB must determine that the potential benefits to research participants are reasonable in relation to the potential risks. Very often, research at Brown does not include potential direct benefits to participants, but may only benefit society as a whole by helping researchers.*

The proposed research does not guarantee direct benefits to the participants beyond the opportunity to participate in a scientific enterprise. There is a potential indirect benefit of this research as it may advance understanding of human sensory processing, and the effects of TMS on the human brain. TMS is currently FDA approved for treatment-resistant depression, and is being actively investigated for a wide range of other disorders, including several that affect touch processing (e.g. chronic pain and autism). In this way, this study may ultimately contribute to disease etiology and treatment.

#### PART IV. APPENDICES SCREENER

**Please complete & attach the following Appendices to this Application, as applicable.**

<u>Incl.</u>	<u>N/A</u>	
<input type="checkbox"/>	<input type="checkbox"/>	<a href="#">Appendix A. Children as Subjects</a> <i>To be attached when minors are included as participants [please be aware of the age of majority for your specific research site(s)]</i>
<input type="checkbox"/>	<input type="checkbox"/>	<a href="#">Appendix B. Prisoners as Subjects</a> <i>To be attached when prisoners are included as participants.</i>
<input type="checkbox"/>	<input type="checkbox"/>	<a href="#">Appendix C. Use of Drugs</a> <i>To be attached when the research includes the use of FDA-regulated or unregulated drugs.</i>
<input checked="" type="checkbox"/>	<input type="checkbox"/>	<a href="#">Appendix D. Use of Devices</a> <i>To be attached when the research includes the use of FDA-regulated or unregulated devices.</i>
<input type="checkbox"/>	<input type="checkbox"/>	<a href="#">Appendix E. Prescription Drug / Medication Management</a> <i>To be attached when study procedures include administering prescription medications to study participants.</i>
<input type="checkbox"/>	<input type="checkbox"/>	<a href="#">Appendix F. Mental Health Safety Plan</a> <i>To be attached when participants may experience significant emotional distress, or be at risk of themselves or others.</i>

## PART V. INFORMED CONSENT

Informed consent is a *process*, not just a form. The IRB must ensure the informed consent process clearly discloses and facilitates the understanding of all information needed to make an informed decision to participate while promoting the voluntariness of participation.

Please review the [Consent/assent templates](#) and related guidance on the HRPP Forms & Templates page before developing your consent forms.

### 1. Describe the informed consent process, including:

Following arrival at the research site for their initial MRI session, informed consent will be obtained according to IRB guidelines, in person, by a researcher who has successfully completed the Brown University Education Program in the Protection of Human Research Participants (CITI program), and who is knowledgeable about the study. This may include [REDACTED] The consenting process will take place in a private testing room in close proximity to the site of the experimental session. Prior to consent, the participant will be informed of her/his rights as a research participant, any known risks involved in the experimental methodologies, any benefits to the participant, and information regarding the study procedures. The participant's consent will be documented on an IRB approved consent form. The standard consent form to be used for this study is attached. If the participant is interested in participating in other studies, these studies may be mentioned and/or screened for during the consent procedure.

### 2. Facilitate Understanding

During the consenting process, the participant will be encouraged to ask questions about anything they do not understand, and the researcher will verbally ask if they fully understand the study procedures and consent form before signing. The researcher will also remind the participant at the beginning of each study session that they can stop the session/study at any time, and are not required to come back for subsequent sessions.

### 3. Documentation

Participants will be asked to sign a copy of the consent form that the researcher will keep on file in a locked storage cabinet. A second copy of the consent form will be provided to study participants to keep.

### 4. Additional Considerations

All study participants will be consented. This study does not involve any deception, and all data will be de-identified.

Proceed to [PART VII. DATA SECURITY ASSESSMENT](#)

## PART VI. USE OF SECONDARY DATA / BIOSPECIMENS

1. From what source(s) will you acquire or access the data / biospecimens?

n/a

2. Do any of the source(s) require a Data Use Agreement (DUA) or other Agreement that requires institutional signature to obtain, access or use the data / biospecimens? ☐ Yes ☒ No

*If "yes," please include a copy of the Agreement(s) with this submission and also follow the [Data Use Agreement review and signature processes](#).*

n/a

3. Describe the type(s) of data and date range(s) of the data you will use and the characteristics of the study research population (e.g., age range, sex, and any other pertinent demographic information.)

n/a

Proceed to [PART VII. DATA SECURITY ASSESSMENT](#)

## PART VII. DATA SECURITY ASSESSMENT

### 1. Do the study data / biospecimens include identifiers? Video and audio recordings are considered identifiable.

☒ Yes ☐ No

If "yes," answer the following questions. If "no," you are not required to complete this Part of the application. Proceed to [Part VIII](#).

A. Describe the identifiers associated with the data / biospecimens.

MRI data (including header information) will not include any patient identifiers. Data stored in the Brown MRF PACS and study data used by the lab will be referred to using participant IDs only.

EEG data will not contain patient identifiers, and will be associated with participant IDs only.

Study consent forms and questionnaires will be associated with participant names and questionnaires will list participant birthdates.

B. Justify why identifiers are required to conduct the research.

Identifiers are required in the consent forms because participants are required to sign their names on these forms. Identifiers are required on the screening questionnaires in order to facilitate the recruitment and screening process.

C. Describe the proposed research use of the identifiable data / biospecimens.

The only identifiable study data will be in our recruitment/screening questionnaires. As participant identifying information is not relevant to the study after participants take part in research sessions, this information will be converted to electronic format and associated only with the participant ID after data collection is complete. Paper forms with participant names will be kept in a locked storage cabinet in a locked room following conversion to electronic format with participant identifiers removed.

D. Self-classify the [Risk Level](#) of these data / biospecimens (select the *highest level of risk* for all data / biospecimens being collected).

☐ [Level 1 Risk](#)

☒ [Level 2 Risk](#)

☐ [Level 3 Risk](#)

### 2. How will study data / biospecimens be [collected](#)?

- ☒ Brown desktop
- ☒ Laptop
- ☐ [Departmental server](#)
- ☐ [CIS managed server](#)
- ☐ [Brown Qualtrics](#)
- ☐ [REDCap](#); Please describe what instance of REDCap is being used (Brown does not have an instance of REDCap): [Click here to enter text.](#)
- ☐ MTurk (AMT)
- ☐ Text messaging → You must complete the [Text messaging](#) section after completing Qs 3 – 5.
- ☐ Mobile App (on tablet, iPad, Phone) → You must complete the [Mobile App](#) section after completing Qs 3-5.
- ☐ [Zoom](#)
- ☐ Other audio / videoconferencing tool; please describe the tool:
- ☒ Paper records, including photographs. Please describe, including how you will securely store the paper records: Subject's identifiable information (i.e. screening questionnaires) will be stored separately from individual data. Paper records will be maintained in locked file cabinets in locked offices.
- ☐ Web-based site / survey / other tool not listed above → You must complete the [Web-based Other](#) section after completing Qs 3 – 5.
- ☐ Other; please describe:

### 3. Who will have access to the study data / biospecimens?

- ☐ A. Brown PI only. How will unauthorized access by others be prevented?
- ☒ B. Brown PI and other Brown research team members. How will unauthorized access by others be prevented?  
  
All MRI, EEG and electronic data will not contain participant identifying information- it will be referred to using a participant identification ID only once transcribed electronically following initial paper collection. All paper records (i.e. consent forms and screening questionnaires) will be kept in a locked cabinet inside a locked office.
- ☐ C. Data will be shared with research collaborators external to Brown. This data sharing intent **must** be described as part of your consent process / form. Please describe how you will securely share / transfer the data outside of Brown:

*Note that an Outgoing Data Use Agreement is required when sharing identifiable data external to Brown. Please follow the procedures outlined [here](#). You do not need to submit a copy of a DUA to the HRPP. This will be linked by the ORI administratively.*

### 4. Where will the study data / biospecimens be stored?

<input type="checkbox"/> <a href="#">Departmental server</a> <input checked="" type="checkbox"/> <a href="#">CIS managed server</a> <input type="checkbox"/> <a href="#">Stronghold</a> <input checked="" type="checkbox"/> <a href="#">Campus file storage</a> <input type="checkbox"/> <a href="#">REDCap</a> <input checked="" type="checkbox"/> Other. Please describe: Locally on Brown University laptop
<b>5. If traveling with your data, describe how your data will be secured.</b>
All electronically collected data (EEG, MRI and electronically transcribed questionnaires) will lack participant identifying information. If it is necessary to travel with this data, it will be on a password-protected computer or accessed directly from Brown University's Network via Brown's Virtual Private Network (VPN).
<b>6. For how long will you retain identifiable data / biospecimens? How will you destroy identifiers when no longer required?</b>
Identifiable data in the form of screening questionnaires and consent forms will be kept for at least 5 years after the cessation of the study. Identifiers will be removed from screening surveys using black-out marker following cessation of data collection.
<b>Text Messaging (only complete if instructed above.)</b>
1. Are you using the current text messaging service available on the device?
<input type="checkbox"/> Yes <input type="checkbox"/> No      If "no," you must also complete the <a href="#">Mobile App</a> section.
2. Whose device will be used? <input type="checkbox"/> Participant's personal phone <input type="checkbox"/> Brown-issued phone
3. Content of messaging: (If brief, insert here; otherwise, please provide as an attachment)
4. Is the communication one-way or two-way? <input type="checkbox"/> One-way <input type="checkbox"/> Two-way
<b>Mobile App (only complete if instructed above.)</b>
1. Name of the mobile app:
2. Has this site / tool been reviewed by CIS IT Security?
<input type="checkbox"/> Yes <input type="checkbox"/> No      If "no," answer the following: a. Who created the site / tool (vendor name or off the-shelf app creator name)? b. Where is it hosted? c. Is the site / tool scanned for security vulnerabilities? <input type="checkbox"/> Yes <input type="checkbox"/> No d. What version of software is being used, if applicable: <input type="checkbox"/> N/A or e. How are the data encrypted?
3. Whose device will be used? <input type="checkbox"/> Participant's personal phone <input type="checkbox"/> Brown-issued phone If Participant's person phone: a. How is the app downloaded to the device? b. Is a password or PIN required for the app? <input type="checkbox"/> Yes <input type="checkbox"/> No
4. Will data be stored on the device for any period of time?
<input type="checkbox"/> Yes <input type="checkbox"/> No      a. If "yes," please describe (i.e., queue on phone and then transmitted to server):  b. Is the app data encrypted on the device? <input type="checkbox"/> Yes <input type="checkbox"/> No

5. Device features mobile app can access <input type="checkbox"/> N/A <input type="checkbox"/> Device ID and call information <input type="checkbox"/> Identity <input type="checkbox"/> Contacts <input type="checkbox"/> Camera <input type="checkbox"/> SMS or chat <input type="checkbox"/> Storage <input type="checkbox"/> Device and application history <input type="checkbox"/> Phone <input type="checkbox"/> Photo / media / files <input type="checkbox"/> Microphone <input type="checkbox"/> Location <input type="checkbox"/> Other; please describe:	
6. Will a third-party have access to research data through this app? <input type="checkbox"/> Yes <input type="checkbox"/> No	
7. Is data transmitted by the device?	
<input type="checkbox"/> Yes <input type="checkbox"/> No	If "yes," how is it encrypted in transit?
8. Are phone numbers or mobile identification numbers stored with the data? <input type="checkbox"/> Yes <input type="checkbox"/> No	
<b>Web-based Other (only complete if instructed above.)</b>	
1. Name of the site / tool:	
2. Has this site / tool been reviewed by CIS IT Security?	
<input type="checkbox"/> Yes <input type="checkbox"/> No	If "no," answer the following: a. Who created the site / tool (vendor name or off the-shelf app creator name)? b. Where is it hosted? c. Is the site / tool scanned for security vulnerabilities? <input type="checkbox"/> Yes <input type="checkbox"/> No d. What version of software is being used, if applicable: <input type="checkbox"/> N/A or e. How are the data encrypted?
<input type="checkbox"/> Yes <input type="checkbox"/> No	If "no," answer the following: a. Who created the site / tool (vendor name)? b. Where is it hosted? c. Is the site / tool scanned for security vulnerabilities? <input type="checkbox"/> Yes <input type="checkbox"/> No d. What version of software is being used, if applicable: <input type="checkbox"/> N/A or e. How are the data encrypted?
3. Is informed consent being obtained via this site / tool?	
<input type="checkbox"/> Yes <input type="checkbox"/> No	If "yes," how is re-identification prevented?
4. Does the technology allow for the explicit exclusion of the collection of IP address of the participant's connection?	
<input type="checkbox"/> Yes <input type="checkbox"/> No	If "yes," will you use this option to exclude the collection of IP address? <input type="checkbox"/> Yes <input type="checkbox"/> No

Brown Qualtrics: CIS has pre-vetted [Brown Qualtrics](#) for collection/storage of up to [Risk Level III data](#). Qualtrics is the preferred survey tool for all Brown research data collection.

REDCap: Brown does not currently have its own instance of REDCap. Access to REDCap through a Lifespan collaborator must be explicitly identified.

Data collection: The expectation is that data collection *devices* will only store data during active data collection. Data must then be transitioned to more secure long-term storage solutions.

Departmental/CIS managed servers: If data are collected/entered directly onto a Departmental or CIS managed server, **you must ensure** that the server meets the security standards described in the [Minimum Security Standards for Servers](#) based on the Risk Level of the data identified in 1D.

Proceed to [PART VIII. INTERNATIONAL RESEARCH](#)

## PART VIII. INTERNATIONAL RESEARCH

### 1. Does the research involve human subjects activities outside of the United States?

☐ Yes ☒ No

a. If "yes," please list the countries. If "no," you are not required to complete this Part of the application. Proceed to [PART IX. ATTACHMENTS](#).

b. What is the status of permissions / approvals from local ethics boards or committees?

☐ Received; please append to this Application.

☐ Pending

☐ N/A. Please explain:

c. Will this research take place in a non-public setting (including a school, hospital or clinic) for which local permission is required? ☐ Yes ☐ No  
If "yes," please append a letter(s) of support or permission(s) to this Application.

d. Describe how you have taken into account any social, political, or cultural issues that may impact participants.

- ☐ I have reviewed the current version of the [International Compilation of Human Research Standards](#) and agree to abide by relevant local laws, regulations and guidelines.
- ☐ I have reviewed the [General Data Protection Regulations guidance](#) and will abide by any requirements.
- ☐ I have reviewed ORI's export control guidance on [international travel](#), [international collaborations](#), and [international shipping](#) (if applicable)

Proceed to [PART IX. ATTACHMENTS](#)

## PART IX. ATTACHMENTS

**Please attach the following materials to this Application for Full Board / Expedited IRB Review, as applicable.**

Incl.	N/A	
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Informed consent documents / scripts
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Data collection materials (questionnaires, surveys, interview scripts, etc.)
<input type="checkbox"/>	<input checked="" type="checkbox"/>	Permissions, approval documents, and/or support letters identified in PART VII.
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Recruitment materials (emails, flyers, letters, scripts, posters, brochures, etc.)
<input type="checkbox"/>	<input checked="" type="checkbox"/>	Application for IRB Authorization Agreement
<input type="checkbox"/>	<input checked="" type="checkbox"/>	Data Use Agreement from data provider(s)
<input type="checkbox"/>	<input checked="" type="checkbox"/>	Data Safety Monitoring Plan
<input type="checkbox"/>	<input checked="" type="checkbox"/>	Other:

## PART X. CONFLICT OF INTEREST

[The Brown University Conflict of Interest Policy for Officers of Instruction and Research](#) ("COI Policy") defines the term "Investigator" as "the project director or principal investigator and any other person, regardless of title or position (e.g., full or part-time faculty member, staff member, student, trainee, collaborator, or consultant), who is **responsible** for the **design, conduct, or reporting** of sponsored research."

Using this definition of "Investigator," please ensure that all Investigators on this protocol answer questions (1) and (2) below. Attach additional sheets for any Investigators who are not the PI; additional sheets are available on the HRPP website.

1. Have you completed a conflict of interest disclosure (i.e. *Annual COI Assurance Form* or *COI Reporting Form*) within the past 12 months and is it accurate and up-to-date as of the time of this submission, as required by Brown's [COI Policy](#)? (You may access the InfoEd system [here](#) to confirm.)

☒ Yes ☐ No      If "no," please do so before submitting this Application

2. Do you have a [significant financial interest](#) (SFI) that is related to this research protocol? "Related" could mean the research involves products, technology, intellectual property, or services made, owned, or provided by the entity/ies in which you have an SFI. It could also mean that the SFI could be affected by the proposed research or its results.

☐ Yes ☒ No      If "yes," please identify the SFI and explain the relatedness:

<input type="checkbox"/>	Additional COI sheets for Investigators are attached to this Application.
--------------------------	---

## PART XI. INVESTIGATOR & FACULTY ADVISOR AGREEMENTS / PRINCIPAL INVESTIGATOR RESPONSIBILITIES

### A. Conduct of the Research

1. I accept responsibility for the ethical conduct of this research and protection of participants as set forth in the [Belmont Report](#), [Common Rule](#), and Brown University policies.
2. I accept responsibility for ensuring this research is conducted in accordance with:
  - a) Sound research design and methods;
  - b) The parameters of the research plan and activities described in this Application;
  - c) The applicable terms of the grant, contract, or other signed funding agreements;
  - d) Applicable laws and regulations, including those protecting the rights, safety and welfare of human subjects.
3. I certify that I am, or my faculty advisor is, sufficiently qualified by education, training and experience to assume responsibility for the proper conduct of this research. I accept responsibility for ensuring that all member of the research team have or will complete human subjects [CITI training](#) before any work with participants or identifiable data / biospecimens begins.
4. I accept responsibility to personally conduct and/or directly supervise this research. I certify that I have sufficient time and resources to properly conduct and/or supervise this research.

### B. Ensuring and Maintaining Compliance

1. I will comply with relevant regulatory and institutional reporting requirements, including Brown University's [Reportable Events Policy](#).
2. I understand that it is my responsibility to ensure that any research personnel, including myself, responsible for the design, conduct or reporting of the research declares any conflicts of interest related to this research. I will ensure that any changes that impact my or other research personnel's answers to the questions in PART IX. Conflict of Interest, are reported promptly to Brown's HRPP.
3. I will ensure that prospective agreement and/or informed consent is obtained and a copy is provided to participants, when appropriate.
4. If there are changes to the research described in this Application for Full Board / Expedited IRB Review that may impact the study's classification as Full Board or Expedited research, I will promptly notify the Brown HRPP of such changes.
5. I will notify the Brown HRPP when I have completed all activities involving human subjects or identifiable participant data or identifiable biospecimens.
6. I will maintain approval, as applicable, with collaborative parties, including approvals from other countries or jurisdictions.

7. I will cooperate with any post-approval monitoring or auditing of study activities and/or study records as requested and/or required by the Brown ORI, the Brown IRB, funding entities, sponsors, and/or any federal or state regulatory agencies.

### **C. Study records, Reports and Documentation**

1. I will maintain all research protocol materials and consent materials for the duration of this study.
2. I will maintain research records for at least three years following the end of this research, or for a longer length of time if specified in applicable regulations or sponsor requirements. I will take measures to prevent accidental or premature destruction of these records.
3. I will abide by all terms of any Data Use Agreement (or equivalent agreement) related to this study, including those agreed to electronically (through an online attestation).
4. I will ensure that the data security measures for acquisition, collection, transfer and use of study data described in PART VI. of this Application are adhered to by all members of the research team.

**By my signature below, I certify that I have read and agree to uphold all of you and/or Advisor Responsibilities in PART XI.**

**Principal Investigator signature:**

**Date:** [Click here to enter a date.](#)

**An Advisor's signature is required for all graduate/medical student projects**

**Advisor certifies the following:** Advisor has read the complete protocol, approves this project, and will remain available to advise the student throughout the course of the proposed human subjects research, or will transfer responsibilities to another Advisor if unable to advise for the entirety of the project.

**Advisor's name (please print):**

**Advisor's signature:**

**Date:** [Click here to enter a date.](#)

***For HRPP/IRB Use Only***

**Signature of the HRPP:**

**Date of HRPP determination/Limited IRB Review approval:** [Click here to enter a date.](#)

## Medical Devices/ Investigator Checklist

Protocol title: The causal role of neocortical beta events in human sensory perception

PI name: Stephanie R. Jones, PhD

Date: January 31, 2019

A device will **NOT** fall under the FDA regulations if all of the following statements are true:

- 1) Data will not be submitted to the FDA
- 2) Safety and/or effectiveness data will not be collected about the device
- 3) The device is used only as a tool to collect data to examine a physiologic principle


If ALL statements above are true, please initial here: \_\_\_\_\_SRJ\_\_\_\_\_

**Please include this form and the device manual in your protocol submission to the IRB. No further information is required at this time.**

This checklist serves as a guide to Sponsor-Investigators in determining and documenting information required by the IRB related to the use of a medical device which falls under the FDA regulations (21 CFR812) in a human subjects' research study and requires an Investigational Device Exemption (IDE). **\*Sponsor-Investigator is the individual who initiates and also conducts the study/clinical investigation. Typically this is the Principal Investigator (PI). A sponsor-investigator must comply with regulatory requirements applicable to both sponsors and clinical investigators (21 CFR312.3).** A device will fall under the FDA regulations if data will be submitted to the FDA **OR** safety and/or effectiveness data are collected about the device.

The IDE regulations (21 CFR812) describe three types of device studies: significant risk (SR), which require an IDE application approved by the FDA, non-significant risk (NSR) which must follow the abbreviated IDE requirements (21 CFR812.2b) and do not require a submission of an IDE application to the FDA or exempt from IDE regulations (21 CFR812.2b30. Please consult the cited regulations for additional information on these types of device studies.

Attached to this form is a flowchart that may also be helpful in determining if an IDE is required.

I.	Device name: Brown University MRF Siemens 3T PRISMA MRI Scanner			HRPP USE ONLY: Confirm information for IRB review, (based on protocol submission and checklist) noting a check mark 
a.	Studies considered exempt from IDE regulations include:			
	<ul style="list-style-type: none"> <li>A legally marketed device when used in accordance with its' labeling.</li> </ul>	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
	<ul style="list-style-type: none"> <li>A diagnostic device if it complies with labeling in 809.10(c) and the testing is noninvasive, does not require an invasive sampling procedure that presents significant risk, does not by design or intention introduce energy into a subject, and is not used a diagnostic procedure without confirmation by another medically established diagnostic product or procedure.</li> </ul>	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
	<ul style="list-style-type: none"> <li>Consumer preference testing, testing of a modification or testing of a combination of devices if the device(s) have an approved Premarket Notification 510(k), or are exempt from 510(k) <b>AND</b> if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.</li> </ul>	<input type="checkbox"/> Yes	<input type="checkbox"/> No	

	<p>If "Yes" to one of the bulleted items, the study is exempt from IDE regulations. Please provide/attach supporting documentation, e.g., letter from the FDA, or other information used to make this exempt determination. This form is complete. If "No" to all bulleted items, continue to next item.</p>			
<b>b</b>	<p>Does the research collect safety and/or efficacy data on medical devices in human participants or on human specimens?</p> <p>(An IDE must be submitted to the FDA if the sponsor-investigator intends to conduct a clinical investigation with an investigational new device to determine safety and effectiveness <b>unless</b> the investigation is considered to have an approved application for an IDE, or is exempt from the IDE requirements. ( 21 CFR 812.2)</p>	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
<b>c</b>	<p>Has the FDA assessed the device for a risk determination? If yes, Please indicate if the FDA determination is: NSR _____ (non-significant risk) SR _____ (significant risk) *If "yes", provide the IRB with a copy of the FDA documentation, and this form is complete, the remaining items do not apply.</p>	* <input type="checkbox"/> Yes	<input type="checkbox"/> No	
<b>d</b>	<p>Has the sponsor-investigator made a risk determination? If yes, Please indicate if the determination is: NSR _____ (non-significant risk) SR _____ (significant risk)</p> <p>Please provide the IRB with a description of the device, reports of prior investigations with the device, the proposed investigational plan, and any other information that will assist the IRB in the review of this determination.</p>	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
<b>e</b>	<p>Please provide the plan to securely obtain store, dispense/use, and dispose of the device. Attach a separate document that includes this information or note the location/section/page # where this information may be found in the protocol</p>			
<b>f</b>	<p>The informed consent process/document must include a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained <b>and the possibility that the FDA may inspect the records.</b> (21 CFR 50.25 (a) (5))</p>			
<b>g</b>	<p>Is the study an applicable clinical trial?</p> <p><i>"Applicable clinical trials" generally include:</i></p> <p>(1) Trials of Drugs and Biologics: <i>Controlled, clinical investigations, other than Phase 1 investigations, of a product subject to FDA regulation;</i></p> <p>(2) Trials of Devices: <i>Controlled trials with health outcomes, other than small feasibility studies, and pediatric post-market surveillance.</i> Complete statutory definitions and more detailed information on the NIH's current thinking about the meaning of "applicable clinical trials" may be found in the <a href="#">"Elaboration of Definitions of Responsible Party and Applicable Clinical Trial"</a>.</p> <p>(if No, skip h)</p>	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
<b>h</b>	<p>Is the clinical trial registered in Clinicaltrials.gov?</p>	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
	<ul style="list-style-type: none"> <li>Under federal regulation 21 CFR 50.25(c) the following statement must be reproduced word-for-word in informed consent documents for applicable clinical trials begun after March 7, 2012: "A description of this clinical trial will be available on <a href="http://www.ClinicalTrials.gov">http://www.ClinicalTrials.gov</a>, as required by US Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time"</li> </ul>			
	<p>Notes:</p>			

## Medical Devices/ Investigator Checklist

Protocol title: The causal role of neocortical beta events in human sensory perception

PI name: Stephanie R. Jones, PhD

Date: January 31, 2019

A device will **NOT** fall under the FDA regulations if all of the following statements are true:

- 1) Data will not be submitted to the FDA
- 2) Safety and/or effectiveness data will not be collected about the device
- 3) The device is used only as a tool to collect data to examine a physiologic principle


If ALL statements above are true, please initial here: \_\_\_\_\_SRJ\_\_\_\_\_

**Please include this form and the device manual in your protocol submission to the IRB. No further information is required at this time.**

This checklist serves as a guide to Sponsor-Investigators in determining and documenting information required by the IRB related to the use of a medical device which falls under the FDA regulations (21 CFR812) in a human subjects' research study and requires an Investigational Device Exemption (IDE). **\*Sponsor-Investigator is the individual who initiates and also conducts the study/clinical investigation. Typically this is the Principal Investigator (PI). A sponsor-investigator must comply with regulatory requirements applicable to both sponsors and clinical investigators (21 CFR312.3).** A device will fall under the FDA regulations if data will be submitted to the FDA **OR** safety and/or effectiveness data are collected about the device.

The IDE regulations (21 CFR812) describe three types of device studies: significant risk (SR), which require an IDE application approved by the FDA, non-significant risk (NSR) which must follow the abbreviated IDE requirements (21 CFR812.2b) and do not require a submission of an IDE application to the FDA or exempt from IDE regulations (21 CFR812.2b30. Please consult the cited regulations for additional information on these types of device studies.

Attached to this form is a flowchart that may also be helpful in determining if an IDE is required.

<b>I.</b>	Device name: Brain Vision electroencephalography (EEG)			<b>HRPP USE ONLY:</b> Confirm information for IRB review, (based on protocol submission and checklist) noting a check mark 
<b>a.</b>	Studies considered exempt from IDE regulations include:			
	<ul style="list-style-type: none"> <li>A legally marketed device when used in accordance with its' labeling.</li> </ul>	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
	<ul style="list-style-type: none"> <li>A diagnostic device if it complies with labeling in 809.10(c) and the testing is noninvasive, does not require an invasive sampling procedure that presents significant risk, does not by design or intention introduce energy into a subject, and is not used a diagnostic procedure without confirmation by another medically established diagnostic product or procedure.</li> </ul>	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
	<ul style="list-style-type: none"> <li>Consumer preference testing, testing of a modification or testing of a combination of devices if the device(s) have an approved Premarket Notification 510(k), or are exempt from 510(k) <b>AND</b> if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.</li> </ul>	<input type="checkbox"/> Yes	<input type="checkbox"/> No	

	<p>If "Yes" to one of the bulleted items, the study is exempt from IDE regulations. Please provide/attach supporting documentation, e.g., letter from the FDA, or other information used to make this exempt determination. This form is complete. If "No" to all bulleted items, continue to next item.</p>			
<b>b</b>	<p>Does the research collect safety and/or efficacy data on medical devices in human participants or on human specimens?</p> <p>(An IDE must be submitted to the FDA if the sponsor-investigator intends to conduct a clinical investigation with an investigational new device to determine safety and effectiveness <b>unless</b> the investigation is considered to have an approved application for an IDE, or is exempt from the IDE requirements. ( 21 CFR 812.2)</p>	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
<b>c</b>	<p>Has the FDA assessed the device for a risk determination? If yes, Please indicate if the FDA determination is: NSR _____ (non-significant risk) SR _____ (significant risk) *If "yes", provide the IRB with a copy of the FDA documentation, and this form is complete, the remaining items do not apply.</p>	* <input type="checkbox"/> Yes	<input type="checkbox"/> No	
<b>d</b>	<p>Has the sponsor-investigator made a risk determination? If yes, Please indicate if the determination is: NSR _____ (non-significant risk) SR _____ (significant risk)</p> <p>Please provide the IRB with a description of the device, reports of prior investigations with the device, the proposed investigational plan, and any other information that will assist the IRB in the review of this determination.</p>	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
<b>e</b>	<p>Please provide the plan to securely obtain store, dispense/use, and dispose of the device. Attach a separate document that includes this information or note the location/section/page # where this information may be found in the protocol</p>			
<b>f</b>	<p>The informed consent process/document must include a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained <b>and the possibility that the FDA may inspect the records.</b> (21 CFR 50.25 (a) (5))</p>			
<b>g</b>	<p>Is the study an applicable clinical trial?</p> <p><i>"Applicable clinical trials" generally include:</i></p> <p>(1) Trials of Drugs and Biologics: <i>Controlled, clinical investigations, other than Phase 1 investigations, of a product subject to FDA regulation;</i></p> <p>(2) Trials of Devices: <i>Controlled trials with health outcomes, other than small feasibility studies, and pediatric post-market surveillance.</i> Complete statutory definitions and more detailed information on the NIH's current thinking about the meaning of "applicable clinical trials" may be found in the <a href="#"><i>"Elaboration of Definitions of Responsible Party and Applicable Clinical Trial"</i></a>.</p> <p>(if No, skip h)</p>	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
<b>h</b>	<p>Is the clinical trial registered in Clinicaltrials.gov?</p>	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
	<ul style="list-style-type: none"> <li>Under federal regulation 21 CFR 50.25(c) the following statement must be reproduced word-for-word in informed consent documents for applicable clinical trials begun after March 7, 2012: "A description of this clinical trial will be available on <a href="http://www.ClinicalTrials.gov">http://www.ClinicalTrials.gov</a>, as required by US Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time"</li> </ul>			
	<p>Notes:</p>			

## Medical Devices/ Investigator Checklist

Protocol title: The causal role of neocortical beta events in human sensory perception

PI name: Stephanie R. Jones, PhD

Date: January 31, 2019

A device will **NOT** fall under the FDA regulations if all of the following statements are true:

- 1) Data will not be submitted to the FDA
- 2) Safety and/or effectiveness data will not be collected about the device
- 3) The device is used only as a tool to collect data to examine a physiologic principle


If ALL statements above are true, please initial here: \_\_\_\_\_SRJ\_\_\_\_\_

**Please include this form and the device manual in your protocol submission to the IRB. No further information is required at this time.**

This checklist serves as a guide to Sponsor-Investigators in determining and documenting information required by the IRB related to the use of a medical device which falls under the FDA regulations (21 CFR812) in a human subjects' research study and requires an Investigational Device Exemption (IDE). **\*Sponsor-Investigator is the individual who initiates and also conducts the study/clinical investigation. Typically this is the Principal Investigator (PI). A sponsor-investigator must comply with regulatory requirements applicable to both sponsors and clinical investigators (21 CFR312.3).** A device will fall under the FDA regulations if data will be submitted to the FDA **OR** safety and/or effectiveness data are collected about the device.

The IDE regulations (21 CFR812) describe three types of device studies: significant risk (SR), which require an IDE application approved by the FDA, non-significant risk (NSR) which must follow the abbreviated IDE requirements (21 CFR812.2b) and do not require a submission of an IDE application to the FDA or exempt from IDE regulations (21 CFR812.2b30. Please consult the cited regulations for additional information on these types of device studies.

Attached to this form is a flowchart that may also be helpful in determining if an IDE is required.

<b>I.</b>	Device name: Magstim transcranial magnetic stimulation			HRPP USE ONLY: Confirm information for IRB review, (based on protocol submission and checklist) noting a check mark 
<b>a.</b>	Studies considered exempt from IDE regulations include:			
	<ul style="list-style-type: none"> <li>A legally marketed device when used in accordance with its' labeling.</li> </ul>	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
	<ul style="list-style-type: none"> <li>A diagnostic device if it complies with labeling in 809.10(c) and the testing is noninvasive, does not require an invasive sampling procedure that presents significant risk, does not by design or intention introduce energy into a subject, and is not used a diagnostic procedure without confirmation by another medically established diagnostic product or procedure.</li> </ul>	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
	<ul style="list-style-type: none"> <li>Consumer preference testing, testing of a modification or testing of a combination of devices if the device(s) have an approved Premarket Notification 510(k), or are exempt from 510(k) <b>AND</b> if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.</li> </ul>	<input type="checkbox"/> Yes	<input type="checkbox"/> No	

	<b>If "Yes" to one of the bulleted items, the study is exempt from IDE regulations. Please provide/attach supporting documentation, e.g., letter from the FDA, or other information used to make this exempt determination. This form is complete. If "No" to all bulleted items, continue to next item.</b>			
<b>b</b>	Does the research collect safety and/or efficacy data on medical devices in human participants or on human specimens?  (An IDE must be submitted to the FDA if the sponsor-investigator intends to conduct a clinical investigation with an investigational new device to determine safety and effectiveness <b>unless</b> the investigation is considered to have an approved application for an IDE, or is exempt from the IDE requirements. ( 21 CFR 812.2)	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
<b>c</b>	Has the FDA assessed the device for a risk determination? If yes, Please indicate if the FDA determination is: NSR _____ (non-significant risk) SR _____ (significant risk) *If "yes", provide the IRB with a copy of the FDA documentation, and this form is complete, the remaining items do not apply.	* <input type="checkbox"/> Yes	<input type="checkbox"/> No	
<b>d</b>	Has the sponsor-investigator made a risk determination?  If yes, Please indicate if the determination is: NSR _____ (non-significant risk) SR _____ (significant risk)  Please provide the IRB with a description of the device, reports of prior investigations with the device, the proposed investigational plan, and any other information that will assist the IRB in the review of this determination.	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
<b>e</b>	Please provide the plan to securely obtain store, dispense/use, and dispose of the device. Attach a separate document that includes this information or note the location/section/page # where this information may be found in the protocol			
<b>f</b>	The informed consent process/document must include a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained <b>and the possibility that the FDA may inspect the records.</b> (21 CFR 50.25 (a) (5))			
<b>g</b>	Is the study an applicable clinical trial?  <i>"Applicable clinical trials" generally include:</i>  (1) Trials of Drugs and Biologics: <i>Controlled, clinical investigations, other than Phase 1 investigations, of a product subject to FDA regulation;</i>  (2) Trials of Devices: <i>Controlled trials with health outcomes, other than small feasibility studies, and pediatric post-market surveillance.</i> <i>Complete statutory definitions and more detailed information on the NIH's current thinking about the meaning of "applicable clinical trials" may be found in the <a href="#">"Elaboration of Definitions of Responsible Party and Applicable Clinical Trial"</a>.</i>  (if No, skip h)	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
<b>h</b>	Is the clinical trial registered in Clinicaltrials.gov?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
	<ul style="list-style-type: none"> <li>Under federal regulation 21 CFR 50.25(c) the following statement must be reproduced word-for-word in informed consent documents for applicable clinical trials begun after March 7, 2012: "A description of this clinical trial will be available on <a href="http://www.ClinicalTrials.gov">http://www.ClinicalTrials.gov</a>, as required by US Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time"</li> </ul>			
	Notes:			

## Appendix D: Use of Devices Investigator Checklist

Protocol title: The causal role of neocortical beta events in human sensory perception

PI name: Stephanie R. Jones, PhD

Date: February 9, 2021

**Investigations with multiple devices must submit a separate form for each device.**

Device name: Magstim EMG Interface Module

A device will **NOT** fall under the FDA regulations if all of the following statements are true:


- 1) Data will not be submitted to the FDA
- 2) Safety and/or effectiveness data will not be collected about the device
- 3) The device is used only as a tool to collect data to examine a physiologic principle

If ALL statements above are true, please initial here: SRJ

**Please include this form and the device manual in your protocol submission to the IRB. No further information is required at this time.**

This checklist serves as a guide to Sponsor-Investigators in determining and documenting information required by the IRB related to the use of a medical device which falls under the FDA regulations (21 CFR812) in a human subjects' research study and requires an Investigational Device Exemption (IDE). **\*Sponsor-Investigator is the individual who initiates and also conducts the regulatory requirements applicable to both sponsors and clinical investigators (21 CFR312.3).** A device will fall under the FDA regulations if data will be submitted to the FDA **OR** safety and/or effectiveness data are collected about the device.

The IDE regulations (21 CFR812) describe three types of device studies: significant risk (SR), which require an IDE application approved by the FDA, non-significant risk (NSR) which must follow the abbreviated IDE requirements (21 CFR812.2b) and do not require a submission of an IDE application to the FDA or exempt from IDE regulations (21 CFR812.2b30). Please consult the cited regulations for additional information on these types of device studies.

	For additional guidance, <a href="#">this flowchart</a> may be helpful in determining if an IDE is required.			<b>HRPP USE ONLY:</b> Confirm information for IRB review, (based on protocol submission and checklist) noting a check mark 
<b>a.</b>	Studies considered exempt from IDE regulations include:			
	<ul style="list-style-type: none"> <li>A legally marketed device when used in accordance with its' labeling.</li> </ul>	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
	<ul style="list-style-type: none"> <li>A diagnostic device if it complies with labeling in 809.10(c) and the testing is noninvasive, does not require an invasive sampling procedure that presents significant risk, does not by design or intention introduce energy into a subject, and is not used a diagnostic procedure without confirmation by another medically established diagnostic product or procedure.</li> </ul>	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
	<ul style="list-style-type: none"> <li>Consumer preference testing, testing of a modification or testing of a combination of devices if the device(s) have an approved Premarket Notification 510(k), or are exempt from 510(k) <b>AND</b> if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.</li> </ul>	<input type="checkbox"/> Yes	<input type="checkbox"/> No	

	<b>If "Yes" to one of the bulleted items, the study is exempt from IDE regulations. Please provide/attach supporting documentation, e.g., letter from the FDA, or other information used to make this exempt determination. This form is complete. If "No" to all bulleted items, continue to next item.</b>			
<b>b</b>	Does the research collect safety and/or efficacy data on medical devices in human participants or on human specimens?  (An IDE must be submitted to the FDA if the sponsor-investigator intends to conduct a clinical investigation with an investigational new device to determine safety and effectiveness <b>unless</b> the investigation is considered to have an approved application for an IDE, or is exempt from the IDE requirements. ( 21 CFR 812.2)	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
<b>c</b>	Has the FDA assessed the device for a risk determination? If yes, Please indicate if the FDA determination is: NSR _____ (non-significant risk) SR _____ (significant risk) *If "yes", provide the IRB with a copy of the FDA documentation, and this form is complete, the remaining items do not apply.	* <input type="checkbox"/> Yes	<input type="checkbox"/> No	
<b>d</b>	Has the sponsor-investigator made a risk determination?  If yes, Please indicate if the determination is: NSR _____ (non-significant risk) SR _____ (significant risk)  Please provide the IRB with a description of the device, reports of prior investigations with the device, the proposed investigational plan, and any other information that will assist the IRB in the review of this determination.	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
<b>e</b>	Please provide the plan to securely obtain store, dispense/use, and dispose of the device. Attach a separate document that includes this information or note the location/section/page # where this information may be found in the protocol			
<b>f</b>	The informed consent process/document must include a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained <b>and the possibility that the FDA may inspect the records.</b> (21 CFR 50.25 (a) (5))			
<b>g</b>	Is the study an applicable clinical trial?  "Applicable clinical trials" generally include:  (1) Trials of Drugs and Biologics: <i>Controlled, clinical investigations, other than Phase 1 investigations, of a product subject to FDA regulation;</i>  (2) Trials of Devices: <i>Controlled trials with health outcomes, other than small feasibility studies, and pediatric post-market surveillance.</i> Complete statutory definitions and more detailed information on the NIH's current thinking about the meaning of "applicable clinical trials" may be found in the <a href="#">"Elaboration of Definitions of Responsible Party and Applicable Clinical Trial"</a> .  (if No, skip h)	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
<b>h</b>	Is the clinical trial registered in Clinicaltrials.gov?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
	<ul style="list-style-type: none"> <li>Under federal regulation 21 CFR 50.25(c) the following statement must be reproduced word-for-word in informed consent documents for applicable clinical trials begun after March 7, 2012: "A description of this clinical trial will be available on <a href="http://www.ClinicalTrials.gov">http://www.ClinicalTrials.gov</a>, as required by US Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time"</li> </ul>			
	Notes:			



## Magstim® Stimulator Interface Module Operating Manual

MOP52-EN  
Revision 02



CE  
2797

## TABLE OF CONTENTS

Table of Contents.....	i
Guarantee .....	ii
Section 1 Introduction .....	1
1.1 Indications for Use.....	1
1.2 Contraindications .....	1
1.3 Devices Covered .....	1
1.4 Compatibility .....	1
1.5 Frequently Used Functions.....	2
Section 2 Warnings and Precautions .....	3
Section 3 Product Descriptions .....	4
3.1 Front view .....	4
3.2 Rear view .....	5
3.3 Top view .....	6
Section 4 Operating Instructions .....	7
4.1 Connection .....	7
4.2 Triggering Options .....	7
4.3 Pulse Width Options.....	8
Section 5 Maintenance.....	9
5.1 User Maintenance and Calibration .....	9
5.2 Cleaning and Disinfecting* .....	9
5.3 Servicing .....	9
5.4 Device Lifetime .....	9
5.5 Disposal .....	9
Section 6 Specifications .....	10
6.1 Safety Specifications .....	10
6.2 Technical Specifications.....	10
6.3 Environmental Conditions* .....	10
6.4 Packing Instructions.....	10
Section 7 Contact Details .....	11
7.1 International.....	11
7.2 Authorised representative in the European Community.....	11
7.3 USA .....	11

## GUARANTEE

The Magstim Company Limited guarantees the effectiveness of both materials and workmanship for a period of one year from the date of shipment; for the following products;

Magstim® Stimulator Interface Module

- P/N: 3901-00

The Magstim Company Ltd. reserves the right to perform guarantee services in its factory, at an authorised repair station, or at the customer's installation; at the discretion of the company.

The Magstim Company Ltd. guarantees to repair or replace defective equipment or parts, free of charge within the guarantee period; provided that the said defects occur during normal service. Replacement will be only at the company's discretion where a repair is not possible and/or not feasible.

Claims for damages during shipment must be filed promptly with the transportation company. All correspondence concerning the equipment must specify the model name and/or number, as well as the serial number, exactly as they appear on the equipment invoice.

Improper use, mishandling, tampering with, or operation of the equipment without following operating instructions will void this guarantee and release The Magstim Company Limited from any further obligations under this guarantee.

The Magstim Company Limited will only accept responsibility for effects on safety, reliability and performance of the equipment if:

- modifications or repairs are carried out by persons authorised by The Magstim Company Limited;
- the electrical installation of the relevant room complies with local regulations; and
- the equipment is used in accordance with the instructions for use.

## SECTION 1 INTRODUCTION

**Note:** Where this document refers to IEC Standards, this also applies to the regional variant standards.

### 1.1 Indications for Use

The Magstim® Stimulator Interface Module is intended for use with the Magstim® range of stimulators stated in "1.4 Compatibility". Ensure you have read and familiarized yourself with all sections of the relevant stimulator operating manual/s before use.

The purpose of the Magstim® Stimulator Interface Module is to allow the user to configure various input and output triggering options of the connected stimulator; such as pulse width, edge or level triggering, active high or active low signalling.

**USA Only:** The Magstim® Stimulator Interface Module is considered an investigational device. In accordance with US federal regulations an IDE and/or IRB approval may be required. Use of this accessory with a 510(k) cleared device would be considered off-label use of the device.

### 1.2 Contraindications

The Magstim® Stimulator Interface Module is an accessory to the Magstim® range of stimulators stated in "1.4 Compatibility" and shares the same contraindications. Please refer to the appropriate stimulator operating manual for contraindications.

### 1.3 Devices Covered

This document is applicable to the following device:

- Magstim® Stimulator Interface Module P/N: 3901-00

**Note:** Please also consult any labelling and information accompanying stimulators and other accessories for safety and use information regarding these devices.

### 1.4 Compatibility

The Magstim® Stimulator Interface Module is compatible to the following range of Magstim® stimulators:

- Magstim® 200<sup>2</sup>
- Magstim® BiStim<sup>2</sup>
- Magstim® Rapid<sup>2</sup>
- Magstim® Rapid<sup>2</sup> Therapy System
- Magstim® Super Rapid<sup>2</sup>
- Magstim® Super Rapid<sup>2</sup> Plus<sup>1</sup>

## 1.5 Frequently Used Functions

Frequently used functions as defined during Magstim's usability process are identified with (\*). Frequently used functions are functions of the Rapid<sup>2</sup> that frequently involve user interaction.

## SECTION 2 WARNINGS AND PRECAUTIONS



**Attention Consult Operating Manual:** Consult the operating manual before using this device. Ensure you are familiar with all sections of this operating manual and the appropriate stimulator operating manual prior to use.



**Operating Manual:** Further information can be located in the operating manual. Where this symbol is adjacent to a particular function on the labelling, further information on this function can be found in this operating manual.

**Connections:** Only equipment that meets the relevant IEC standard should be connected to the Magstim® Stimulator Interface Module.

This connection must be configured in compliance with Clause 16 of IEC 60601-1:2005 with the following interface voltage limitation: Max signalling voltage +5.3V; Max voltage with respect to protective earth potential 30V peak

**Electromagnetic Compatibility (EMC):** This product is specified for use as an accessory to the Magstim® 200<sup>2</sup>, Magstim® BiStim<sup>2</sup> and Magstim® Rapid<sup>2</sup> systems. Refer to the Magstim® 200<sup>2</sup>, Magstim® BiStim<sup>2</sup> and Magstim® Rapid<sup>2</sup> systems operating manual for EMC compliance details and restrictions of the use of the whole system.



**Anti Static Protection:** includes static sensitive components: take appropriate precautions

**Damage:** If there are any signs of damage to the Magstim® Stimulator Interface Module or stimulator, or if any parts are damp or wet, they must not be used. If damaged, the Magstim Company Limited should be contacted for servicing and repair (see page 11 for contact details).

**Explosive and Flammable Atmospheres:** The Magstim stimulators and accessories must not be used in an explosive atmosphere, around explosive gases or in the presence of flammable anaesthetics.

**Modification:** No modification of this equipment is allowed.

**Mains Leads:** The Rapid<sup>2</sup> system must be used only with the supplied mains leads fitted with an integral filter, as they are required to maintain the system's compliance with IEC 60601-1-2 regarding Electro-Magnetic emissions.

**Environmental Conditions\*:** The system must not be used or stored under environmental conditions that fall outside those specified in Section 6 of this operating manual.



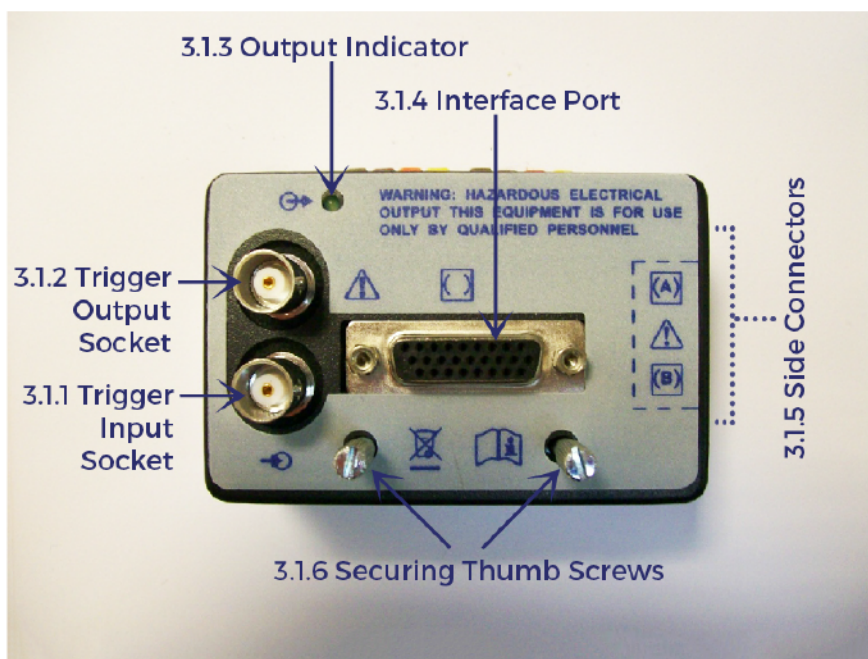
**Do Not dispose in general waste.** See "5.5 Disposal" on page 9

## SECTION 3 PRODUCT DESCRIPTIONS

The Magstim® Stimulator Interface Module facilitates the synchronisation of a compatible Magstim® Stimulator with an external device.

Further to this, the Interface Module allows the user to configure various input and output triggering options of the connected stimulator.

### 3.1 Front view



#### 3.1.1 Trigger Input socket (BNC)

5V CMOS logic levels.

#### 3.1.2 Trigger Output socket (BNC)

5V CMOS logic levels.

#### 3.1.3 Output Indicator

The green LED will flash to indicate a trigger output pulse.

#### 3.1.4 Interface Port

If using a stimulator UI, this connector allows the UI cable to be connected through the interface module. See "4.1 Connection" on page 7.

### 3.1.5 Side connectors (A) (B)

The connectors on the side of the interface module are not currently in use and not required for use.

### 3.1.6 Securing Thumb Screws

The thumb screws are used to secure the connection of the interface module to the stimulator socket. See "4.1 Connection" on page 7.

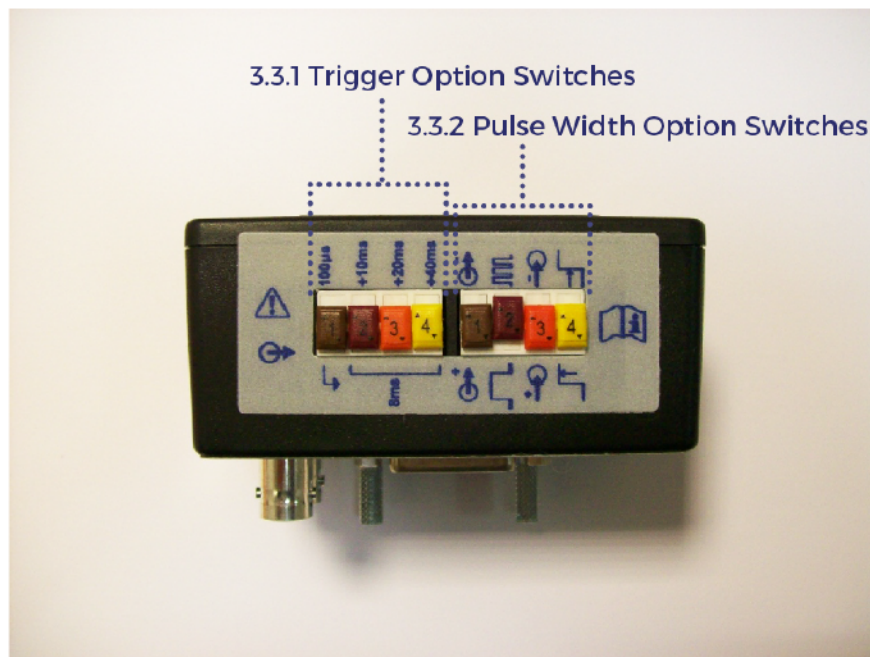
## 3.2 Rear view



### 3.2.1 Interface Module Connector

The connection between the interface module and the stimulator socket. See "4.1 Connection" on page 7.

### 3.3 Top view



#### 3.3.1 Trigger Option Switches

The interface module provides various switches to allow configuration of the stimulation triggering.

Detailed information on the trigger options can be found in “4.2 Triggering Options” on page 7.

#### 3.3.2 Pulse Width Option Switches

The interface module provides various switches to allow configuration of the stimulation pulse width.

Detailed information on the pulse width options can be found in “4.3 Pulse Width Options” on page 8.

## SECTION 4 OPERATING INSTRUCTIONS

### 4.1 Connection

- Align the Interface Module Connector to the external interface port on the rear of the stimulator.

**Note:** The “Interface Module Connector” may also be called an “Isolated interface Port” or “UI Link Socket” in the stimulator manual and is labelled with



- Firmly connect the connector to the port on the stimulator.
- On the front of the interface module, turn the thumb screws until finger tight to secure the module.
- If using, connect the stimulator UI cable to the UI port on the interface module and tighten the thumb screws to secure.

### 4.2 Triggering Options

The switches below can be used to configure signals



#### 4.2.1 Positive / Negative Trigger Out



**Positive Trigger Out** : The interface module will emit an active high output pulse through the trigger out connection.



**Negative Trigger Out** : The interface module will emit an active low output pulse through the trigger out connection.



#### 4.2.2 Output Pulse Trigger



**Per Train** : The interface module will emit 1 output pulse through the trigger out connection, for each stimulation train.



**Per Stimulation Pulse** : The interface module will emit 1 output pulse through the trigger out connection, for each stimulation pulse.



#### 4.2.3 Positive / Negative Trigger In





**Positive Trigger In** : The connected stimulator will trigger when an active high signal level is present to the trigger input of the interface module.



**Negative Trigger In** : The connected stimulator will trigger when an active low signal level is present to the trigger input of the interface module.

#### 4.2.4 Level / Edge Triggering

 **Level Triggering** : In this setting, the connected stimulator will trigger continuously when the conditions of 4.2.3 are maintained (see above).

 **Edge Triggering** : In this setting, the connected stimulator will trigger once, each time the conditions of 4.2.3 are met (see above).

### 4.3 Pulse Width Options

With the stimulator interface module connected the stimulator pulse width can be configured between 8ms & 78ms, or reset to the default 100µs, using a combination of the switches below:

#### 4.3.1 100µs

Set this switch to 100µs (right) to ignore the below switches and set the pulse width to the default 100µs.

Set this switch to the left to set pulse width at 8ms, plus any active switches below.

#### 4.3.2 +10ms

Set this switch to +10ms (right) to add 10ms to the collated pulse width.

#### 4.3.3 +20ms

Set this switch to +20ms (right) to add 20ms to the collated pulse width.

#### 4.3.4 +40ms

Set this switch to +40ms (right) to add 40ms to the collated pulse width.

## SECTION 5 MAINTENANCE

### 5.1 User Maintenance and Calibration

At the start of each session the user must check the Magstim® Stimulator Interface Module for any signs of damage, paying particular attention to the plastic casing.

If there are any signs of damage, the product must not be used and should be returned to The Magstim Company Limited for servicing and repair (see page 11 for contact details).

### 5.2 Cleaning and Disinfecting\*

The Magstim® Stimulator Interface Module cannot be sterilised; therefore, do not allow it to become contaminated with bodily fluids. The Magstim® Stimulator Interface Module may be cleaned using a cloth moistened with 70% isopropyl alcohol in pH neutral water. Ensure it has dried thoroughly before use.

It is the responsibility of the user to ensure the Magstim® Stimulator Interface Module is cleaned when necessary.

### 5.3 Servicing

The Magstim® Stimulator Interface Module contains no user serviceable parts. Servicing of Magstim® Stimulator Interface Module must only be carried out by The Magstim Company Limited or one of its authorised service centres. To arrange a return or for further information, contact the service department (see Section 7).

Service training courses are available to suitably qualified personnel on request. For further information contact the service department (see Section 7).

### 5.4 Device Lifetime

The support lifetime of the Magstim® Stimulator Interface Module is defined as 7 years from the date of shipment. Use beyond this period is not recommended.

Servicing and replacement parts will be available within these times. Magstim® cannot guarantee that spare parts will be available after these times.

### 5.5 Disposal



When the Magstim® Stimulator Interface Module reaches the end of its serviceable life, it should not be disposed of in general waste. Magstim® should be contacted for advice on disposal in compliance with the appropriate environmental regulations. Failure to do so could cause an environmental hazard as a result of decomposition of materials used in its construction.

## SECTION 6 SPECIFICATIONS

### 6.1 Safety Specifications

Protection against Ingress of Liquids	IPx0 (Not Protected)
Protection against flammable anaesthetic mixtures	Not Protected
Protection against electric shock	Type BF Applied Part

### 6.2 Technical Specifications

#### Isolated Interface

Logic High Voltage:	>4.0V
Max Voltage:	5.3V
Logic Low Voltage:	<0.8V
Min Voltage:	-0.3V

All voltages are with respect to Aux Gnd signal on the isolated interface connector

#### General Specifications:

Dimensions:	88mm x 62mm x 60mm (LxWxH)
Weight:	153g

**Note:** All specifications are subject to alteration.

### 6.3 Environmental Conditions\*



Operating temperature:	5°C to 40°C
Transport and storage temperature:	-19°C to 60°C



Operating, transport and storage relative humidity:	10% to 80% (non-condensing)
---	-----------------------------



Operating atmospheric pressure:	80kPa to 106kPa
Transport and storage atmospheric pressure:	50kPa to 106kPa

### 6.4 Packing Instructions

If, for any reason, it is necessary to return your Magstim® Stimulator Interface Module, care should be taken to ensure that the equipment is adequately packed to prevent transit damage. Ideally the equipment should be returned in its original packing. If this or an adequate replacement is not available, replacement shipping cartons can be obtained from the Magstim Company Limited.

The Magstim® Stimulator Interface Module must be completely disconnected before shipping. Failure to do so is likely to result in transit damage.

## SECTION 7 CONTACT DETAILS

### 7.1 International



The Magstim Company Limited  
Spring Gardens, Whitland, Carmarthenshire, SA34 0HR

Telephone: +44 (0)1994 240798  
Fax: +44 (0)1994 240061  
E-mail: [info@magstim.com](mailto:info@magstim.com)

Website: [www.magstim.com](http://www.magstim.com)

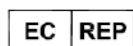
#### Servicing Enquiries

Telephone: +44 (0)1994 242900  
E-mail: [service@magstim.com](mailto:service@magstim.com)

#### Sales Enquiries

Telephone: +44 (0)1994 241111  
E-mail: [sales@magstim.com](mailto:sales@magstim.com)

### 7.2 Authorised representative in the European Community



Technomed Europe  
Amerikalaan 71, 6199 AE Maastricht-Airport, The Netherlands

Telephone: +31 43 408 68 68

### 7.3 USA

Magstim Inc.  
9855 West 78th st. Suite 12, Eden Prairie, MN 55344

Telephone: 612-225-5868  
Toll-Free: 844-MAGSTIM (624-7846)  
Email: [USAsales@magstim.com](mailto:USAsales@magstim.com)

Website: [www.magstim.com](http://www.magstim.com)

#### Servicing Inquiries

Telephone: 844-881-6530  
Email: [USAservice@magstim.com](mailto:USAservice@magstim.com)



August 3, 2018

Magstim Company Ltd.  
Tom Campbell  
Regulatory Affairs Manager  
Spring Gardens  
Whitland, Carmarthenshire  
Wales, UK SA34 0HR

Re: K180907

Trade/Device Name: HORIZON TMS Therapy System  
Regulation Number: 21 CFR 882.5805  
Regulation Name: Repetitive Transcranial Magnetic Stimulation System  
Regulatory Class: Class II  
Product Code: OBP  
Dated: July 2, 2018  
Received: July 5, 2018

Dear Tom Campbell:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm> identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal

statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see <https://www.fda.gov/CombinationProducts/GuidanceRegulatoryInformation/ucm597488.htm>); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to <http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm>.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (<https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/>) and CDRH Learn (<http://www.fda.gov/Training/CDRHLearn>). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (<http://www.fda.gov/DICE>) for more information or contact DICE by email ([DICE@fda.hhs.gov](mailto:DICE@fda.hhs.gov)) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Pamela D.  
Scott -S

Digitally signed by Pamela D. Scott -S  
DN: c=US, o=U.S. Government, ou=FDA, ou=People,  
ou=2018.08.03 18:58:54 -0400, cn=Pamela D. Scott -S

for Carlos L. Peña, PhD, MS  
Director  
Division of Neurological  
and Physical Medicine Devices  
Office of Device Evaluation  
Center for Devices and Radiological Health

Enclosure

## Indications for Use

510(k) Number (if known)

K180907

Device Name

HORIZON™ TMS Therapy System

Indications for Use (Describe)

The HORIZON™ TMS Therapy System is indicated for the treatment of Major Depressive Disorder in adult patients who have failed to achieve satisfactory improvement from prior antidepressant medication in the current episode.

Type of Use (Select one or both, as applicable)

☒ Prescription Use (Part 21 CFR 801 Subpart D)

☐ Over-The-Counter Use (21 CFR 801 Subpart C)

### CONTINUE ON A SEPARATE PAGE IF NEEDED.

This section applies only to requirements of the Paperwork Reduction Act of 1995.

**\*DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.\***

The burden time for this collection of information is estimated to average 79 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services  
Food and Drug Administration  
Office of Chief Information Officer  
Paperwork Reduction Act (PRA) Staff  
[PRASStaff@fda.hhs.gov](mailto:PRASStaff@fda.hhs.gov)

*"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."*



**510(k) SUMMARY**  
**Magstim's HORIZON® TMS Therapy System**

**Submitter's Name, Address, Telephone Number, Contact Person and Date Prepared**

Magstim Company Limited  
Spring Gardens, Whitland, Carmarthenshire  
SA34 0HR, United Kingdom

Phone: +44 (0) 1994 240798  
Facsimile: +44 (0) 1994 240061

Contact Person: Tom Campbell

Date Prepared: July 30, 2018

**Name of Device**

HORIZON® TMS Therapy System

**Common or Usual Name/**

Repetitive Transcranial Magnetic Stimulation (rTMS) System

**Classification**

Repetitive Transcranial Magnetic Stimulation (rTMS) System

21 C.F.R. § 882.5805, Class II, product code OBP

**Predicate Devices**

HORIZON® Therapy System, The Magstim Company Limited. (K171051) (*Primary Predicate*)  
NeuroStar TMS Therapy System, Neuronetics, Inc. (K160703) (*Secondary Predicate*)  
Neurosoft TMS, TeleEMG, LLC. (K173441) (*Secondary Predicate*)

**Device Description**

The HORIZON® TMS Therapy System is a computerized, electromechanical medical device that produces and delivers non-invasive, magnetic stimulation using brief duration rapidly alternating, or pulsed, magnetic fields to induce electrical currents directed at spatially discrete regions of the cerebral cortex. This method of cortical stimulation by application of brief magnetic pulses to the head is known as Transcranial Magnetic Stimulation.

The HORIZON® TMS Therapy System is a non-invasive tool for the stimulation of cortical neurons for the treatment of Major Depressive Disorder in adult patients who have failed to achieve satisfactory improvement from antidepressant medication in the current episode. The HORIZON® TMS Therapy System is used for patient treatment by prescription only under the supervision of a licensed physician. It can be used in both inpatient and outpatient settings, including physicians' offices, clinics, and hospitals.

The HORIZON® TMS Therapy System is an integrated system consisting of a combination of hardware, software, and accessories. Its technological characteristics are described in further detail below.

### **Intended Use / Indications for Use**

The HORIZON® TMS Therapy System is indicated for the treatment of Major Depressive Disorder in adult patients who have failed to achieve satisfactory improvement from prior antidepressant medication in the current episode.

### **Technological Characteristics**

The HORIZON® TMS Therapy System is comprised of the following components:

1. HORIZON® Stimulator
  - a. HORIZON® User Interface;
  - b. HORIZON® Mainframe;
  - c. HORIZON® Power Supply;
  - d. Accessory Cables;
  - e. Accessory Footswitch.
2. Coil for MT Determination
  - a. HORIZON® MT Remote Coil.
3. Coil(s) for Treatment
  - a. HORIZON® AFC;
  - b. HORIZON® E-z Cool Coil.
4. Accessory Cart(s) and Coil Holding Mechanism(s)
  - a. Magstim® Trolley;
  - b. Magstim® Coil Stand(s);
  - c. HORIZON® E-z Cart;
  - d. HORIZON® E-z Arm.
5. Accessory Marking Apparatus
  - a. TMS Patient Caps.

The operator controls the HORIZON® TMS Therapy System via the HORIZON® User Interface, using a graphic LCD panel with touchscreen technology. The operator instructions, given through the HORIZON® User Interface, direct the HORIZON® Mainframe in charging and discharging the device's high voltage discharge capacitor. The discharge is delivered to the patient via the stimulating coil. Motor threshold level can be determined using the HORIZON® MT Remote Coil. Treatment is delivered to the treatment area via either the HORIZON® AFC or the HORIZON® E-z Cool Coil, which is positioned above the treatment area. Positioning, and fixation, of the coil over the treatment area is accomplished using the Coil Holding Mechanism(s). The HORIZON® Power Supply provides power to charge the high voltage capacitor in the HORIZON® Mainframe.

Software documentation for a "moderate" level of concern has been provided.

### **Non-Clinical Testing**

Electrical safety and electromagnetic compatibility ("EMC") testing was conducted on the system to demonstrate that the device is compliant with IEC 60601-1 (Ed. 3.1.) and EN 60601-1-2 (2007). Environmental testing also demonstrated compliance with IEC 60601-1.

EN 60601-1-2 (2007) is not an FDA recognized standard and hence a justification of its equivalence to the appropriate FDA recognized standard for its acceptance has been provided.

The biocompatibility evaluation demonstrated that the stimulation coils meet ISO 10993-1 (2009) standards. In addition, acoustic output measurements have been conducted during IEC 60601-1 (Ed. 3.1) testing to demonstrate safety and performance.

The software verification and validation testing further demonstrated that the software performs as intended and in accordance with specifications. The potential risks of HORIZON® TMS Therapy System have been identified and evaluated in compliance with ISO14971, and the risks were determined to be acceptable, or have been addressed with risk control measures.

As required by FDA's Guidance Document titled "Class II Special Controls Guidance Document: Repetitive Transcranial Magnetic Stimulation (rTMS) Systems", non-clinical testing of the HORIZON® TMS Therapy System included testing of the magnetic field characteristics of the system. The results of this testing demonstrate that the magnetic field characteristics of the HORIZON® TMS Therapy System is substantially equivalent to the primary predicate device, the HORIZON® Therapy System (K171051).

### **Substantial Equivalence**

The HORIZON® TMS Therapy System is substantially equivalent to the primary predicate device, the HORIZON® Therapy System (K171051).

The HORIZON® TMS Therapy System and the primary predicate device (K171051) have identical intended use and indications for use, equivalent principles of operation, as well as the same key technological characteristics.

The technological difference between the HORIZON® TMS Therapy System and the HORIZON® Therapy System (K171051), includes the addition of the HORIZON® E-z Cool Coil, HORIZON® E-z Cart and HORIZON® E-z Arm. These changes raise no new issues of safety or effectiveness. Performance data demonstrates that the HORIZON® TMS Therapy System is as safe and effective as the primary predicate device.

The design of the HORIZON® TMS Therapy System is substantially equivalent to the design of the primary predicate device (K171051), as both systems are based on applying transcranial magnetic stimulation by means of repetitive pulse trains at a predetermined frequency. Both systems use the same mechanism of action, i.e., an electromechanical instrument that produces and delivers brief duration, rapidly alternating (pulsed) magnetic fields to induce electrical currents in localized regions of the prefrontal cortex.

The principles of operation of the HORIZON® TMS Therapy System is equivalent to the HORIZON® Therapy System (K171051). The modification to the device allows a range of inter-train intervals from 11 to 26 seconds, rather than the fixed 26 second duration, which allows a reduction in treatment time from 37.5 minutes to a minimum of 18.8 minutes. The change to this output stimulation parameter is identical to the secondary predicate device, the NeuroStar TMS Therapy System (K160703).

Transcranial magnetic stimulation is enabled in the HORIZON® TMS Therapy System and in the HORIZON® Therapy System (K171051), as both have the same key system

components, consisting of electromagnetic coils, a coil holding mechanism, a TMS stimulator and software. The operation procedure is the same in both the HORIZON® TMS Therapy System and the HORIZON® Therapy System (K171051), consisting of system setup, patient preparation, determination of patients' motor threshold, coil position, and administration of treatment at pre-defined treatment stimulation parameters.

The basic software capabilities related to treatment administration are the same as the primary predicate, the HORIZON® Therapy System (K171051). A notable difference is that the arbitrary upper limit imposed by software for the maximum number of pulses per session (cumulative exposure) has been increased from 6000 to 60,000 in the HORIZON® TMS Therapy System. This is supported by TeleEMG, LLC's Neurosoft TMS (K173441) that is capable of delivering a maximum of 72,000.

The HORIZON® TMS Therapy System meets the same electrical and mechanical safety standards (IEC 60601-1) and the same EMC standards (EN 60601-1-2).

The similarities and minor differences between the HORIZON® TMS Therapy System, the HORIZON® Therapy System (*Primary Predicate*), the NeuroStar TMS Therapy System (*Secondary Predicate*) and the Neurosoft TMS (*Secondary Predicate*) are described in **Table 1**.

## Conclusions

In summary, the intended use and indications for use for the HORIZON® TMS Therapy System and primary predicate device, The HORIZON® Therapy System (K171051) are identical.

Furthermore, the key technological characteristics and principles of operation, including basic design, mechanism of action, specifications and treatment procedure are substantially equivalent.

Non-clinical test data demonstrates that the HORIZON® TMS Therapy System is as safe and effective as the HORIZON® Therapy System (K171051).

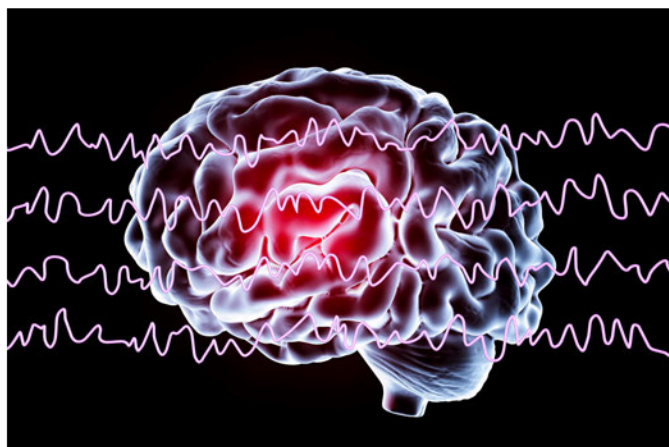
Thus, the HORIZON® TMS Therapy System is considered substantially equivalent to the primary predicate device, the HORIZON® Therapy System (K171051).

**Table 1: Substantial Equivalence Summary**

Criteria	<b>HORIZON® TMS Therapy System</b> (Subject of this submission)	<b>HORIZON® Therapy System</b> (K171051) (Primary Predicate)	<b>NeuroStar TMS Therapy System</b> (K160703) (Secondary Predicate)	<b>Neurosoft TMS</b> (K173441) (Secondary Predicate)
<b>Manufacturer</b>	Magstim Company Limited	Magstim Company Limited	Neuronetics Inc.	TeleEMG, LLC
<b>Device Name</b>	HORIZON® Therapy System	HORIZON® Therapy System	NeuroStar TMS Therapy System	Neurosoft TMS
<b>Clearance date</b>		09/13/2017	06/10/2016	12/13/2017
<b>510(k) number</b>		K171051	K160703	K173441
<b>Device code</b>	OBP	OBP	OBP	OBP
<b>Intended Use/ Indications for Use</b>	The HORIZON® TMS Therapy System is indicated for the treatment of Major Depressive Disorder in adult patients who have failed to achieve satisfactory improvement from prior antidepressant medication in the current episode.	The HORIZON® Therapy System is indicated for the treatment of Major Depressive Disorder in adult patients who have failed to achieve satisfactory improvement from prior antidepressant medication in the current episode.	The NeuroStar TMS Therapy System is indicated for the treatment of Major Depressive Disorder in adult patients who have failed to achieve satisfactory improvement from prior antidepressant medication in the current episode.	The Neurosoft TMS is indicated for the treatment of Major Depressive Disorder in adult patients who have failed to achieve satisfactory improvement from prior antidepressant medication in the current episode.
<b>Magnetic Field Intensity</b>	120% of the MT	120% of the MT	120% of the MT	120% of the MT
<b>Stimulus Frequency</b>	10 Hz	10 Hz	10 Hz	10 Hz
<b>Stimulus Train duration</b>	4 sec	4 sec	4 sec	4 sec
<b>Inter-train interval</b>	11-26 sec	26 sec	11-26 sec	11-26 sec
<b>Number of trains</b>	75	75	75	75
<b>Magnetic Pulses per Session</b>	3000	3000	3000	3000
<b>Treatment Session Duration</b>	18.8 min–37.5 min	37.5 min	18.8 min – 37.5 min	18.8 min–37.5 min

Sessions/week	5			5		5	5
Treatment Schedule	5 daily sessions for 6 weeks			5 daily sessions for 6 weeks		5 daily sessions for 6 weeks	5 daily sessions for 6 weeks
Area of brain to be stimulated	Left Dorsolateral Prefrontal Cortex			Left Dorsolateral Prefrontal Cortex		Left Dorsolateral Prefrontal Cortex	Left Dorsolateral Prefrontal Cortex
	HORIZON® MT Remote Coil	HORIZON® E-z Cool Coil	HORIZON® AFC	HORIZON® MT Remote Coil	HORIZON® AFC	NeuroStar Stimulating Coil	FEC-02-100-C, AFEC- 02-100-C FEC-02-100 (optional), AFEC-02-100 (optional)
Waveform	Biphasic	Biphasic	Biphasic	Biphasic	Biphasic	Biphasic	Biphasic
Core Material	Air	Air	Air	Air	Air	Ferromagnetic core	Air
Pulse Width	330µs	340µs	300µs	330µs	300µs	185µs	280µs
Amplitude in SMT units (Standard Motor Threshold)	0.28 - 1.9			0.28 - 1.9		0.22 - 1.6	FEC-02-100-C 0-1.89 AFEC-02-100-C 0-2.38 FEC-02-100 0-1.92 AFEC-02-100 0-2.33
Frequency range (Hz) at 100%	1 - 20			1 - 20		0.1-30	0.1-30 (stand-alone) 0.1-100 (with PC)
Pulse train duration range (sec)	0.1 - 600			0.1 - 600		1-20	0.5 - 100
Inter-train interval range (sec)	1 - 540			1 - 540		10-60	0 - 300
Maximum # of pulses per session (cumulative exposure)	60000			6000		5000	72000 (Stand-alone) = 2400 s [max session] *30Hz 240000 (with PC) = 2400 s [max session] * 100Hz
Maximum output amplitude (V/m) at a depth of 2cm below the coil surface	150 V/m			150 V/m		135V/m nominal	Not disclosed by Manufacturer

# PARTICIPANTS NEEDED FOR BRAIN RESEARCH STUDY!



The Jones Lab at Brown University is currently looking for healthy adults to participate in a paid research **study investigating brain rhythms and the sense of touch** (Study Protocol #1902002327). We will use non-invasive techniques to record and stimulate brain activity while you do a non-painful computerized task that tests your sense of touch.

## Who is eligible?

- **Healthy, right-handed adults** between 18-65 years of age
- No medical history of seizure, substance dependence, or serious psychiatric, neurological, cardiac, pulmonary or vascular medical issues, no family history of epilepsy
- No metal in the head/neck or implanted electronic devices

## What will you be asked to do?

- Spend approximately **8.5 total hours** on campus at Brown University **over 3 visits**
- Have an **MRI**, then carry out a computerized task while we record electrical activity from your brain using electroencephalography (**EEG**), and receive a type of non-invasive brain stimulation called transcranial magnetic stimulation (**TMS**)

**Compensation:** you will receive up to \$145 for your participation

**If you have *any* questions and/or are interested in participating, please contact** [REDACTED]

Touch Detection Research Study at Brown University [REDACTED]	Touch Detection Research Study at Brown University [REDACTED]	Touch Detection Research Study at Brown University [REDACTED]	Touch Detection Research Study at Brown University [REDACTED]	Touch Detection Research Study at Brown University [REDACTED]	Touch Detection Research Study at Brown University [REDACTED]	Touch Detection Research Study at Brown University [REDACTED]	Touch Detection Research Study at Brown University [REDACTED]	Touch Detection Research Study at Brown University [REDACTED]	Touch Detection Research Study at Brown University [REDACTED]
---	---	---	---	---	---	---	---	---	---

*Wording for Email Mailing Lists & Listservs, including Today@Brown:*

**Subject Line:** Participants Needed for Paid Brain Research Study!

**Full text:** We are currently looking for healthy paid participants to take part in a research study investigating brain rhythms and the sense of touch at Brown University (Study Protocol # 1902002327). We will use non-invasive techniques to record and stimulate brain activity while you do a non-painful computerized task that tests your sense of touch.

Study participants will spend approximately 8.5 hours over 3 visits at the Carney Institute for Brain Science and Magnetic Resonance Facility (MRF) at Brown University, and will be compensated up to \$145 for completing the study.

Eligible participants must be healthy, right-handed adults between 18-65 years of age with no medical history of seizures or family history of epilepsy, no medical history of substance dependence or serious psychiatric, neurological, cardiac, pulmonary or vascular medical issues, and no metal in the head/neck or implanted electronic devices. Certain medications may also make you ineligible for participation – we will discuss this over the phone/email.

Please contact [REDACTED] for more information and/or to discuss participating!

Use of Today@Brown for recruiting participants has been approved by Brown's Human Research Protection Program.

*\*The last line will be used for Today@Brown, but not other email correspondence*



**BROWN UNIVERSITY**





Risks of EEG include minor skin irritation or discomfort from the sensors and gel, and discomfort from sitting still to minimize movement during EEG recording.

The risks of TMS are as follows:

- The TMS itself feels like a light tapping sensation on the head, and you may also feel twitching or contracting of muscles and nerves in the head and face. These effects are temporary and will stop when the stimulation is stopped. You are free to stop at any point during the experiment if you feel any physical or psychological discomfort.
- You may experience head and/or neck pain after the experiment. This is thought to be due to muscle tension from either the TMS itself (see above), or from sitting still for a long period of time. A single dose of acetaminophen or aspirin is recommended if pain persists.
- The TMS coil produces a loud 'click' noise that exceeds sound level safety limits from the Occupational Safety and Health Administration (OSHA), and could produce hearing damage if exposed repeatedly. We require participants and researchers to wear earplugs during the TMS portion of the experiment in order to protect them from this noise.
- Though exceedingly rare even in patients with epilepsy, having a seizure is the most severe adverse event associated with TMS. A seizure is an episode of abnormal brain activity that may also include stiffening of the muscles (often referred to as a "convulsion" or "fit"). The TMS protocol used in this experiment is within accepted safety limits, and we will screen you for pre-existing conditions or medications that could increase your potential seizure risk.
- The TMS creates a magnetic field that can heat up and electrically affect any metal that is implanted in, or worn on, the head and neck. You will be screened for implanted devices (e.g. pacemaker) and other metals in the body, and will be asked to remove metal in and around the head and neck (e.g. necklace) before participating in the study. We will provide a locker where you can secure and lock up your belongings if you'd like.

Prior to the experiment, we will ask you to fill out a questionnaire that will allow us to make sure that (1) our study participant group is representative of the greater population, and (2) that TMS is safe for you. Some of the questions pertain to gender and ethnicity. These questions are included so that we can properly interpret our study results at the population level, and to ensure that we are assessing a fair and representative group from the greater population. Other questions pertain to overall health, mental health status, medications and pregnancy. These questions are for your safety, and your answers will be subsequently anonymized and protected- we will not share this information with anyone other than necessary lab personnel. You may refuse to answer or skip any questions we ask.

You are free to stop at any point during the experiment, for any reason whatsoever. In the event of study-related injury, illness or distress, please contact [REDACTED]

[REDACTED]. You can also reach the study PI, Stephanie Jones, at [REDACTED].

## 6. What are the benefits?

This study provides no direct benefits to you, the participant.

This research will contribute to a greater understanding of human brain activity related to the sense of touch, and the effects of TMS on the human brain. TMS is currently FDA approved for treatment-resistant depression, and is being actively investigated for a wide range of other disorders, including







BROWN

**BROWN UNIVERSITY  
MRI RESEARCH FACILITY**

**INFORMED CONSENT ADDENDUM**

**RISKS AND DISCOMFORTS**

Magnetic Resonance Imaging (MRI) uses a powerful magnet to take pictures of your body. Because the MRI machine exposes the body to a very strong magnetic force, you will have to follow certain safety precautions to make sure you do not have any metal objects in or on your body. Before you undergo your MRI scan, a researcher or technician will ask whether or not your body contains any metallic medical devices or equipment, including heart pacemakers, metal prostheses, implants or surgical clips. You also will be asked whether you have had any prior injury from shrapnel or grinding metal, and you will be asked whether your eyes may have been exposed to metal particles. You or the researcher or technician will also complete a checklist that addresses issues of MRI safety.

If you have no metallic objects or particles in your body, you will be asked before entering the MRI room to remove from your person all metal objects, including jewelry, watches, hair holders, or eyeglasses; and you will be asked to empty your pockets of all materials, including keys, wallets, and magnetic cards such as ATM and credit cards. In addition, you may be asked to change into a hospital gown or other suitable garment. Finally, you may be asked to remove any eye shadow you may be wearing, because eye shadow sometimes contains metallic substances.

MR imaging is generally considered to be safe but accidents, injuries, and even deaths have occurred during MRI procedures. Such adverse events are extremely rare if appropriate safety precautions are followed. Serious complications can occur in people who have pacemakers, metallic particles in their eyes, or certain types of metal prostheses, implants, or surgical clips. MRI is also potentially dangerous for anyone wearing any metal objects, including jewelry, watches, hair holders, eyeglasses or metal on clothing, as well as eye shadow, which sometimes contains metallic substances. In addition, if you enter the MRI room with any magnetic cards, such as ATM and credit cards, you will risk having the data on the cards erased by the MRI machine. For these reasons, a researcher or technician will review safety information with you before the scan. In order to determine whether it is safe for you to undergo the scanning procedure, it will be important that you tell the technician about any metallic objects or devices in or on your body.

During the scan itself, you will lie on a table that slides into a horizontal tube slightly wider than your body. You will be asked to lie still, but you will be able to hear and speak to the MRI personnel/research staff. Some people experience anxiety, panic, or a sensation of claustrophobia when lying in the MRI machine. If you think this may happen to you, please tell the researchers before you have the scan. The scanner also makes loud noises during imaging. Ear protection will be provided to reduce the noise level. If you feel uncomfortable for any reason before or during the procedure, please tell the researchers. If for any reason during the procedure you want to stop, you may do so at any time.

If research devices are being used that are not part of the MRI scanner, such as button response boxes, or equipment that monitors physiological processes, there is a small risk that this equipment or wires attached to this equipment might become hot. Please report any heating/burning sensation immediately. You are encouraged to signal to have the scan stopped at any time if this occurs.

The MRI scanner used for this study has been approved for clinical use by the FDA. However, the investigator may use different radiofrequency pulses or gradients, in which case the MRI may not be considered FDA-approved. Also, some of the operation settings for ordinary clinical circumstances being used to perform scans at the Brown University MRI Research Facility are not approved by the FDA. Nevertheless, there are no known significant risks with this procedure at this time since the radiofrequency magnetic fields and magnetic fields, at the strengths used, are felt to be without harm. There are conservative federal guidelines for radiofrequency magnetic field exposure and our examinations fall within those guidelines.

**FOR WOMEN:** The safety of MR imaging during pregnancy has not been proved. If you are, or might be, pregnant, you cannot take part in this study.

**CAUTION:** This study is neither designed nor intended to detect health problems in participants. The MRI scans that you will undergo do not substitute for an appropriate medical examination by a qualified health care provider. If you suspect that you might be suffering from injury or illness, including any injury involving the head or brain, you should not rely on this study as a way to determine whether or not you are well.

The investigators for this project are not trained to perform radiological diagnosis, and the MRI scans performed in this study are not designed to find abnormalities. The investigators and Brown University are not responsible for failure to find existing abnormalities in your MRI scans. However, on occasion the investigator may notice an MRI image that seems abnormal. When this occurs, the investigator will inform you and recommend that you consult with your primary care physician. The decision whether to proceed with further examination or treatment lies solely with you and your physician. The investigators and Brown University are not responsible for any examination or treatment that you undertake based upon these findings. Because the images collected in this study do not comprise a proper clinical MRI study, these images will not be made available for diagnostic purposes.

#### COMPENSATION IN CASE OF INJURY

Many forms of research involve some risk of injury. In spite of all the care and precautions taken by the investigators, you might develop medical complications from participating in this study. If such complications arise, the researchers will, upon your request, provide information that may be of assistance to you in obtaining appropriate medical treatment. Brown University does not provide financial assistance for medical or other costs. Additionally, Brown University is not responsible for research and medical care by other institutions or personnel participating in this study. You do not waive any liability rights for personal injury by signing this form.

---

Participant signature

---

Date

## Jones Lab TMS - Initial Contact & Screening Form

Name: \_\_\_\_\_

Date: \_\_\_\_\_

Email: \_\_\_\_\_

Birthdate: \_\_\_\_\_

Permission to call? If yes, best time: \_\_\_\_\_

Phone: \_\_\_\_\_

	Please check:	Yes	No
Do we have permission to leave a message on the phone?			
Are you right-handed?			
Are you a fluent English speaker?			
Have you ever had TMS or TCS before?			
Have you ever had an adverse reaction to TMS or TCS?			
Have you ever had a seizure?			
Do you have any family history of epilepsy?			
Have you ever had an unexplained loss of consciousness (i.e. fainting)?			
Do you suffer from chronic or severe headaches?			
Do you have any other cardiac, pulmonary or vascular medical issues?			
Have you ever had a stroke?			
Do you have any brain-related neurological or psychiatric illness?			
Have you been diagnosed with an intellectual/developmental disability or autism spectrum disorder (ASD)?			
Have you ever experienced any hallucinations or delusional behavior?			
Have you ever been diagnosed with any type of substance dependence?			
Have you ever had any serious head/brain injury or concussion?			
Have you ever had any surgery to your head/brain?			
Have you ever had any illness/infection that may cause brain damage?			
Do you have any metal objects/particles in your body (including your eyes)? E.g. metal prostheses, implants, surgical clips, shrapnel, grinding metal			
Do you have any implanted medical devices? E.g. pacemaker, cochlear implant			
Are you taking any medications (including OTCs)?			
Are you pregnant or potentially pregnant?			
Have you experienced any loss of feeling, neuropathy or nerve damage from diabetes, injury or any other cause?			
Do you have chronic pain or fibromyalgia?			
Do you have any pain due to cancer, infection or arthritis?			

**Specify any medical issues, medications & other notes:**

---



---





**Please list any medications you're currently taking:**

---

---

**Have you had any alcohol, nicotine, caffeine or other stimulants today?**

**If so, please indicate how much you had and at what time:**

---

---