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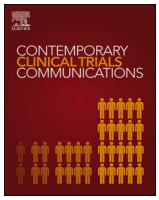

# A mechanistic trial of the neurobiology of extinction learning and intraparietal sulcus stimulation: Protocol

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ABSTRACT

Post-traumatic stress disorder (PTSD) links to impaired extinction learning post-trauma. While treatments like prolonged exposure therapy improve this learning, they benefit only 40–60 % of patients. Optimal arousal supports extinction learning, but excessive arousal can hinder it. The intraparietal sulcus (IPS) is involved in arousal regulation but has not yet been targeted using continuous theta burst stimulation (cTBS) in PTSD. This study is the first to explore the effect of IPS cTBS on extinction learning in PTSD. This study aims to 1) evaluate the impact of IPS cTBS on anxiety potentiated startle (APS) among patients with PTSD compared to sham IPS cTBS, 2) examine whether IPS cTBS improves extinction learning relative to neutral learning, and 3) identify the ideal dose of cTBS. Adults with PTSD will participate in six visits, involving clinical assessments, functional MRI (fMRI), and IPS cTBS. Participants will undergo diagnostic interviews, generate trauma and neutral scripts, and complete script-driven imagery tasks. They will receive active or sham cTBS (counterbalanced) paired with trauma or neutral scripts during separate visits. Follow-up assessments occur at 24 h and 30 days post-intervention. IRB approval and preliminary preparations began in January 2024. Recruitment started in April 2024 and is projected to conclude by April 2028. Ethical procedures are approved by the University of Pennsylvania IRB (Protocol Number: 849571). This will be the first study to evaluate the synergistic effects of extinction training with IPS cTBS in individuals with PTSD. Our findings will strengthen the neurobiological basis of augmenting extinction training with IPS cTBS.

## 1. Introduction

Post-Traumatic Stress Disorder (PTSD) is a costly public health crisis that affects approximately 8 % of the population [1]. Extinction learning, the process of learning that a previously threatening stimulus is no longer dangerous, is central to gold-standard behavioral treatments for PTSD [2–5]. However, individuals with PTSD demonstrate reliable deficits in extinction learning [6,7], and impaired retention following extinction training [8–11]. Deficits in extinction learning and retention contribute to the persistence of fear symptoms and represent a significant challenge to improving treatment outcomes for individuals with PTSD.

Alterations in arousal are a core symptom cluster of PTSD, which may inhibit extinction learning [12,13]. Emotional processing theory has proposed a U-shaped association between arousal and extinction learning [14]. Hyperarousal (i.e., over-engagement) inhibits emotional processing and has been predictive of poorer response to treatment [15,16]. In contrast, hypoarousal ("under-engagement"), an indicator of emotional avoidance during extinction training, is equally problematic for extinction learning and worsens retention of extinction learning [16].

Hyperarousal symptoms are among the most resistant to leading evidence-based treatments for PTSD [17]. Prior work has demonstrated that prolonged exposure therapy (PE), one of the most commonly used treatments based on principles of extinction learning, is inadequate in reducing hyperarousal symptoms and ineffective in 40–67 % of patients [18–20]. Limited prior work has demonstrated some late-emerging reductions in hyperarousal symptoms following treatment [21]. Cognitive

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processing therapy (CPT), another evidence-based PTSD treatment [5], was also shown to be ineffective in reducing hyperarousal symptoms in 26 % of patients [17]. In sum, these findings underscore the importance of directly targeting arousal to optimize therapeutic outcomes. Previous attempts to modulate arousal during extinction learning using medications have yielded mixed results in animal and human studies [22–25]. Prior research has shown that beta-blockers such as propranolol may reduce acute PTSD symptoms during initial extinction training, but not in retention of learning [26]. Another medication, yohimbine, also failed to modulate arousal during extinction learning [27]. These inconsistent findings highlight the need for more targeted strategies to manage arousal during extinction learning.

The intraparietal sulcus (IPS) is a promising neural target for modulating arousal. Research has shown that IPS operates as a connectivity "hub" mediating arousal expression [28,29]. The IPS is functionally connected to the prefrontal cortex (PFC) and amygdala [30,31] during arousal. Most prior neuromodulation trials for PTSD have targeted the prefrontal cortex using repetitive transcranial magnetic stimulation (rTMS), which has demonstrated some improvements in arousal symptoms [32]. However, no research has explored IPS neuromodulation in patients with PTSD or anxiety disorders [33]. Fluctuations in arousal with treatment are associated with differences in neural connectivity compared to other PTSD symptom clusters, suggesting that different neural targets for treatment augmentation may be needed [34]. Given that the IPS serves as a critical region underlying the regulation of arousal [35] and anxiety expression [33,34], neurostimulation of this region may be a novel target for modulating arousal during extinction training.

Continuous theta burst (cTBS), a novel neuromodulation technique, has the potential to modulate IPS activity and arousal associated with PTSD. Previous research has shown that augmenting extinction training with TMS may be beneficial in reducing PTSD symptoms [36,37]. It is thought that cTBS induces long-term depression-like changes in synaptic plasticity [38,39] resulting in decreases in cortical excitability at the site of stimulation [40–42]. TMS to the medial PFC plus extinction training was found to outperform TMS following a neutral cue and sham stimulation after extinction training in improving intrusive symptoms [4]. However, PFC stimulation did not modulate arousal and there was no significant decrease in arousal symptoms. By targeting the IPS, which is functionally linked to arousal regulation, cTBS might address this gap [28–31,43,44].

Compared to traditional rTMS, cTBS has several advantages. cTBS can rapidly alter synaptic plasticity, with immediate effects that dissipate after 60–90 min [40,45–47]. This brief duration is ideal for augmenting extinction learning and evaluating retention of extinction learning. Furthermore, the dose of cTBS can be easily manipulated [48] allowing for individualized dosing of stimulation. Furthermore, cTBS is highly tolerable and safe [49–51]. Given its efficacy, efficiency, flexibility, and tolerability, IPS cTBS has great potential for implementation in real-world settings. This will be the first study to evaluate the synergistic effects of extinction training with IPS cTBS in individuals with PTSD.

### 1.1. Objectives

This study has three core objectives. First, we aim to evaluate the optimal dose of IPS cTBS. Based on our pilot research, we hypothesize that our dose/response analysis will reveal that attenuation of startle for IPS cTBS will plateau at 1200 pulses during training sessions. Second, we aim to compare the main effect of IPS cTBS and its interaction with extinction training on arousal (measured by startle response). We expect that IPS cTBS will result in significantly greater reduction in arousal compared to sham cTBS, as demonstrated by a steeper reduction in startle during cTBS sessions and lower startle during learning retention tests. We hypothesize that participants who receive IPS cTBS will have greater reductions in startle in training and a significantly lower difference in retention of extinction learning vs. control/neutral learning (indicative of greater retention of extinction learning) compared to participants who receive sham cTBS. As a secondary aim, we will test analogous hypotheses on subjective outcomes (subjective units of distress) and on cognitive outcomes (negative outcome expectancy) using the same design, and we hypothesize similar directions of effects. Finally, we aim to evaluate neural mechanisms of action of IPS cTBS + extinction training. We hypothesize that we will observe attenuated activation (relative to pre-test) of the IPS for participants who received IPS cTBS compared to those who received sham cTBS and this effect will be stronger at test of retention of extinction learning relative to neutral learning.

## 2. Methods

### 2.1. Study design

We will recruit participants with PTSD ($N = 120$) using a 2 (between subject: active vs. sham IPS cTBS) x 2 (within subject: trauma vs. neutral script driven-imagery) x 4 (within-subject dose in pulses: 0 vs. 600 vs. 1200 vs. 1800) design (See Fig. 1 for timeline of study visits). Following a baseline evaluation, eligible participants will complete a baseline fMRI scan (T1, T2, DWI, and resting state) to determine the precise location for IPS stimulation. During this scan, we will collect fMRI during threat of unpredictable shock, using a group-based IPS target site (Day 2). Participants will also complete a color-word Stroop task while undergoing fMRI scanning. Then, participants will complete an extinction learning or neutral learning task (within-subjects, counterbalanced) with either active or sham IPS cTBS pulses between blocks of learning trials (Day 4). Twenty-four hours later, they will return to complete a test of retention of extinction or neutral learning and will undergo fMRI scanning (Day 5). After a thirty-day washout period, participants will return to complete two additional visits identical to Day 4 & 5 (Day 34 & 35).

### 2.2. Participants and enrollment procedures

**Eligibility Criteria.** Participants will 1) be adults aged 18–60 recruited from the Philadelphia Metropolitan Area; and 2) meet criteria for PTSD per the Clinician-Administered PTSD Scale for DSM-5 (i.e., scores $\geq$23; [52]). Prospective participants will be excluded if they 1) are pregnant or trying to become pregnant; 2) have a diagnosed seizure disorder or epilepsy; 3) are at increased risk of seizure; 4) are unable or do not consent to speak English; 5) have a medical condition that increases the risk for fMRI or cTBS; 7) have a medical implant; 8) endorse hearing loss; 9) report claustrophobia; 10) report medication or therapy changes within eight weeks of study evaluation; or 11) meet criteria for a current severe substance use disorder.

### 2.3. Recruitment, screening, and enrollment

Recruitment will occur through internal clinic referrals at the University of Pennsylvania Center for the Treatment and Study of Anxiety (CTSA). We will also recruit through online recruitment platforms including the internal Penn Patient Recruiting Management System and through the BuildClinical online research recruiting platform. Finally, we will recruit from the Philadelphia community through targeted advertisements and referral streams at community clinics through established collaborations [53,54]. We project that we will reach our recruitment goal within four years of beginning enrollment.

**Phone Screening.** Participants who appear to meet preliminarily eligibility criteria via the online screening process will complete a brief, additional phone screening with a study team member. During the phone screening, participants will provide their physical address and emergency contact information in case of safety concerns during the study. If preliminarily eligible, prospective participants will then be

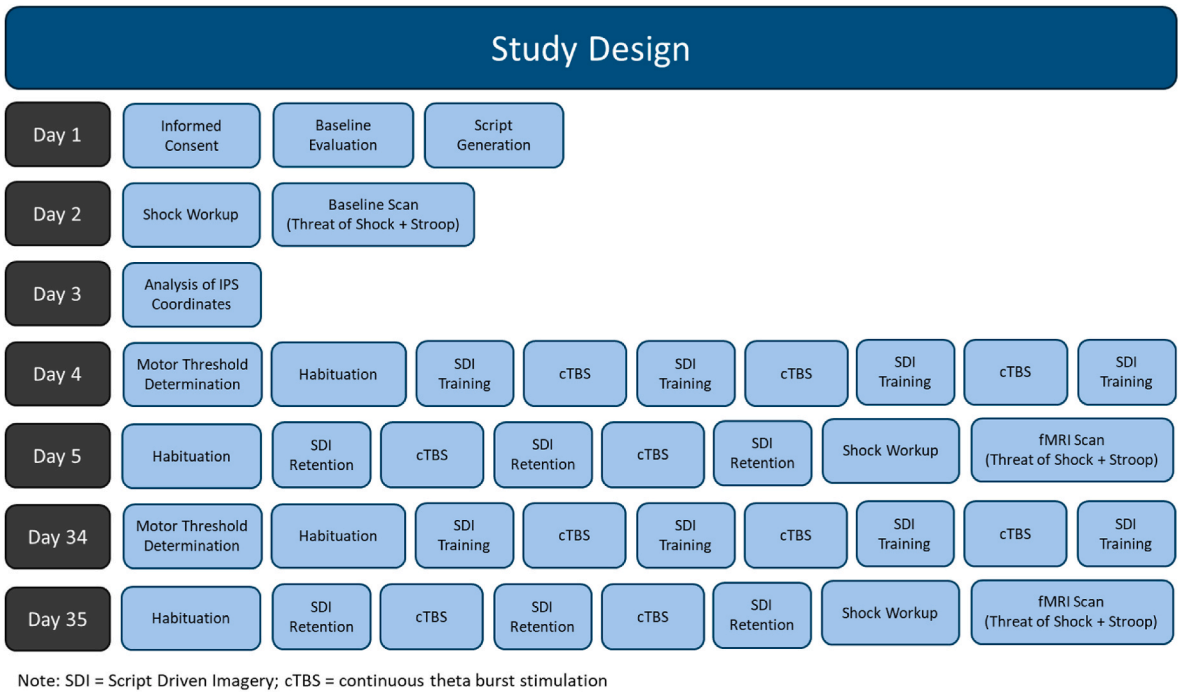


**Fig. 1.** Timeline of study visits.

scheduled for a baseline evaluation.

**Baseline Evaluation.** Prospective participants will complete the informed consent process and a full clinical evaluation with a doctoral-level clinical interviewer. PTSD symptoms will be evaluated using the Clinician-Administered PTSD Scale for DSM-5 Revised (CAPS-5R; [55]) Scores will also be converted to standard scoring on the CAPS-5; [52]). Participants will also complete the Structured Clinical Interview for DSM-5 (SCID-5; [56]) to assess for other psychiatric disorders, and the Columbia-Suicide Severity Rating Scale (C-SSRS; [57]) to assess lifetime suicidal ideation and attempts. Clinical interviewers will be masked to treatment conditions, trained to fidelity in the CAPS-5R and SCID administration, and complete monthly reliability meetings to reduce rater drift. During the baseline evaluation, participants will also generate scripts of a traumatic and neutral life event that the primary investigator will turn into audio recordings for future visits. Finally, participants will complete self-report measures of mental health symptoms (Table 1).

**Script Driven Imagery.** Trauma and neutral scripts were developed using established procedures [58,59]. At baseline, the clinical interviewer instructed participants to write 5–7 sentence scripts in first-person, present tense, describing the events in vivid detail. Trauma scripts focused on the most distressing portion of the Criterion A event identified during the CAPS-5 interview, while neutral scripts described a non-emotional personal event that occurred within a year of the trauma. Participants then selected up to five emotional and physical reactions associated with the event. The PI converted each script into a 30-s audio recording, which participants heard during Days 4, 5, 34, and 35. In this protocol, trauma SDI trials served as the extinction learning condition, whereas neutral SDI trials served as the neutral learning condition. Script order was counterbalanced so that participants completed four SDI training trials with one script on Day 4 and four with the other on Day 34. On each trial, participants were instructed to either "Relax" or "Imagine" the script they heard. Participants then completed three SDI retention trials for each script on Days 5 and 35.

**Table 1**
Study measures.

| | Day in Study | | | | | |
|---|---|---|---|---|---|---|
| | Day in Study | | | | | |
| | 1 | 2 | 4 | 5 | 34 | 35 |
| Eligibility | x | | | | | |
| Clinician Administered PTSD Scale- 5 (CAPS-5) | x | | | | | |
| Structured Clinical Interview for DSM-5 Disorders (SCID-5) | x | | | | | |
| Depression Anxiety Stress Scales-21 (DASS-21) | x | | | | | |
| Generalized Anxiety Disorder-7 (GAD-7) | x | | | | | x |
| Posttraumatic Diagnostic Scale (PDS) | x | | | x | | x |
| Columbia-Suicide Severity Rating Scale (C-SSRS) | x | | | x | | x |
| Patient Health Questionnaire-9 (PHQ-9) | x | | | | | x |
| World Health Organization Disability Assessment Schedule (WHO-DAS) | x | | | | | x |
| Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) Cross-Cutting Baseline Survey | x | | | | | |
| Attentional Control Survey | x | | | | | |
| Sex Hormone Survey | x | | | | | |
| National Institutes of Mental Health (NIMH) Research Subject List | x | | | | | |
| Post-Study Questionnaire | | | | | | x |
| Primary Outcome | | | | | | |
| Startle | | | x | x | x | x |
| Secondary Outcomes | | | | | | |
| Negative Expectancy | | | x | x | x | x |
| Script Driven Imagery (SDI) Training Data | | | x | | x | |
| Script Driven Imagery (SDI) Retention Data | | | | x | | x |
| Threat of Shock | | x | | x | | x |
| Stroop Task | | x | | x | | x |
| Resting State fMRI | | x | | x | | x |
| Subjective Units of Distress Scale (SUDS) | | | x | x | x | x |
| Adverse Events | | x | x | x | x | x |

## 2.4. Randomization

Following baseline evaluation, enrolled participants will be randomized to active or sham cTBS through REDCap's randomization module. Each condition was randomly labeled "Coil A" and "Coil B″ prior to the start of the study to ensure that stimulation remains double-blinded. IPS stimulation has been shown to reduce arousal even after controlling for participants' prediction about whether they received

active or sham stimulation [29]. This study will use additional blinding procedures to ensure the delivery of scalp stimulations to mimic those in active stimulation (See Sham cTBS Section below).

### 2.5. cTBS procedures

**Stimulation Parameters.** Each participant's resting motor threshold will be determined using EMG recordings and the adaptive parameter estimation by sequential testing (PEST) [60] algorithm to ensure accuracy and reproducibility. TMS will be applied at 100 % RMT stimulation intensity for probe conditions.

**Active cTBS.** For both active and sham cTBS, we will use the Magventure Cool B65 A/P coil. cTBS will be delivered at the individually targeted IPS site at 100 % RMT. We have opted to use individually targeted IPS site delivery given that this strategy has evidence for superior efficacy relative to fixed-group average coordinates [61] and has been successfully used with cTBS in prior research [62]. The stimulation pattern and total number of pulses will be triplet 50 Hz bursts, repeated at intervals of 200 ms (5 Hz) continuously for a total of 40s.

**Sham cTBS.** Sham stimulation with the Cool B65 A/P coil works by blocking the magnetic field with an internal spacer on the sham side, allowing the operator to place the appropriate coil surface (active vs. sham) against the scalp. During the sham cTBS, we will use the coil's electric stimulation functionality that allows for the delivery of a brief electric pulse to the scalp simultaneous to the TMS pulse to mimic the active stimulation. The electric pulse is calibrated to the stimulator output to ensure a realistic sham. One limitation to this approach is that the operator typically needs to set the electric stimulation intensity, which does not allow for double-blind scalp e-stim delivery. To account for this, we fabricated a set of custom visually identical cables allowing the operator to deliver real or sham electric stimulation, meaning each subject will receive either active cTBS + sham electric stimulation or sham cTBS + active electric stimulation, allowing for a truly double-blind design. Another limitation of this scalp e-stim approach is that the IPS stimulation site is typically covered with hair, making it difficult to get a low impedance connection with the scalp using typical vinyl surface electrodes. Thus, we will use TMS compatible EEG donut electrodes, secured under the swim cap at the site of stimulation, to deliver the scalp e-stimulation. We will test the impedance of the electrodes and ensure that they are under 10 kΩ.

### 2.6. fMRI procedures

**Threat of shock task.** Consistent with prior studies [28], we used the gold standard, Threat of Shock task as a probe of reactivity to elevated repeat threat. The threat of shock task is administered on Days 2, 5, and 35, and participants will always the shock work-up before each threat of shock-task to determine the proper shock level. Subjects will be presented with 4 alternating blocks of safety and threat (Fig. 2). The block type will be explicitly cued using a colored circle (e.g., orange = threat, blue = safe), and participants will be explicitly informed prior to the experiment which color indicates threat. Throughout the 10 min run, which will be repeated twice, subjects will continuously rate their anxiety using an online visual analog scale. Up to 4 shocks will be delivered using the Digitimer DS7A at random points during the threat blocks per run (two total runs). The order of the blocks will be counterbalanced across subjects. The Threat of shock task will be administered during the baseline scan on Day 2, as well as during follow-up scans on Day 5 and 35.

**Color-Word Stroop.** In the scanner, participants will complete the Color-Word Stroop Task [63], which assesses inhibition of cognitive interference when one stimulus feature prevents the processing of a second feature (the Stroop effect; [64]; Fig. 3). The Stroop task was administered to assess cognitive control under non-threatening conditions, providing a comparison to performance during the unpredictable threat of shock task, which elicits heightened arousal and defensive responding. The Stroop task demonstrates the interference of word meaning on the naming of the color in which the words are written, measured by reaction time, between congruent and incongruent trials. Words are presented in either congruent trials (the word “blue” presented in blue font) or incongruent trials (the word “green” presented in blue font) with two response options for all trials. Participants are given color words written in color and are asked to indicate (with a button press on a response box) the color of the word (not its meaning) by key press as fast as they can without making too many errors. The task includes 4 colors (red, green, blue, and yellow) presented with two types of congruency (congruent or incongruent). Following a 30s rest block, participants complete three alternating blocks of cycles of congruent and incongruent trials, followed by another 30s rest block and then three additional blocks of congruent and incongruent trials, followed by a final 30s rest block. Each experimental block is comprised of fifteen trials randomly shuffled across participants. Stimuli remain on the screen until the participant provides a response and latencies are measured from stimulus onset. This task will be repeated on Days 5 and

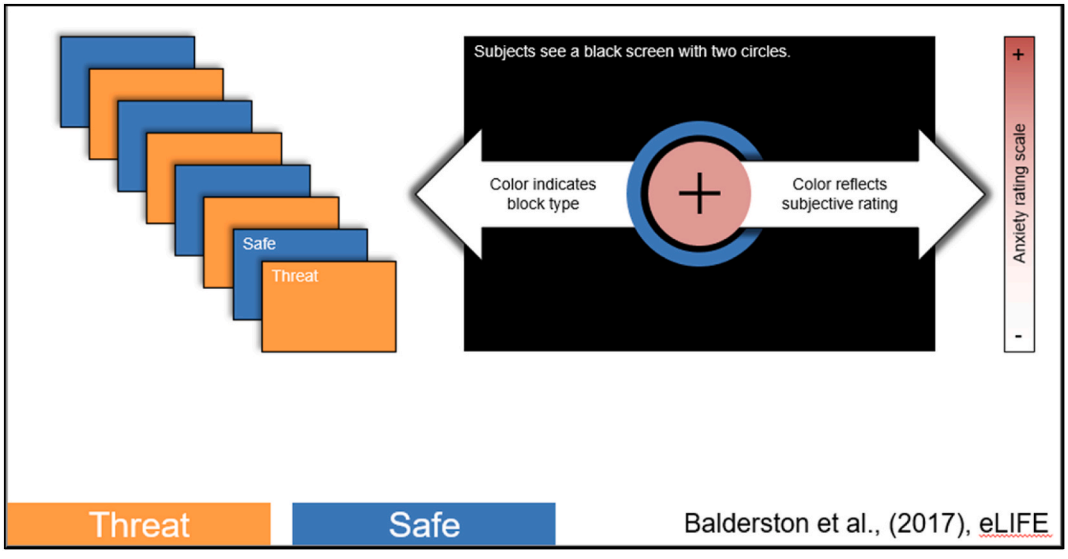


**Fig. 2.** Task design for the Threat of Shock Task.

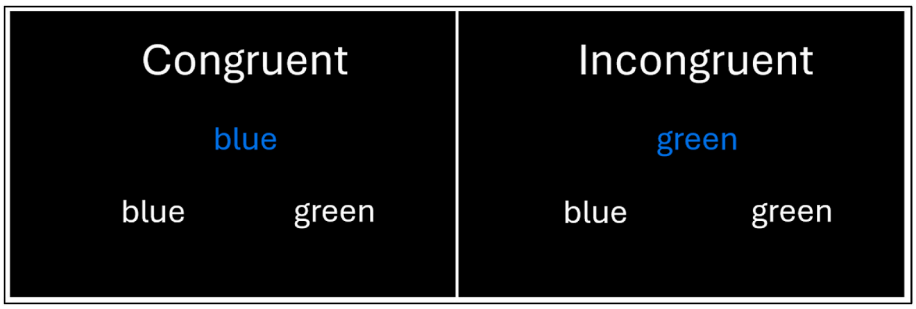


**Fig. 3.** Task design for the Color-Word Stroop Task.

35.

**Neuroimaging acquisition.** MRI data will be acquired on a 3 T S Prisma scanner using one head coil (64 channel; Erlangen, Germany). In the targeting session, we will collect T1-weighted, T2-weighted, diffusion MRI, multiband/multi-echo fMRI scans for the two tasks (2 × 8 min, each). Scan time is 1 h, and participants have 3 total scans. We will use optimize cTBS coil positioning using fMRI by computing a detailed head mesh for electric field calculation and electric field models to optimize stimulation, and we will monitor coil placement using online

**fMRI Processing.** Standard Multi-echo fMRI preprocessing will be conducted using the AFNI software package [65,66]. Steps include slice-time correction, despiking, volume registration, TE-dependent ICA denoising (to remove non-BOLD artifacts), masking, blurring, scaling, motion scrubbing, T1-EPI alignment, and normalization (using MNI template). Additional noise covariates corresponding to white matter and CSF will be regressed out of the resting state timeseries.

**Individualized targeting of cTBS to IPS.** Global brain connectivity (GBC) will be conducted on the cleaned time series, with each voxel in the brain correlated with every other voxel, and correlations averaged across columns to yield a single whole-brain GBC map that reflects the average connectivity between each voxel and the rest of the brain. GBC maps will then be sampled using the IPS maps, and the voxel in the IPS with the largest GBC value will be chosen as the cTBS target [29]. Targeting reliability is important to ensure reproducible results. To accomplish this, the current protocol uses a targeting approach that incorporates a group-level mask to narrow the search space for the personalized target to ensure that the personalized target fall within the IPS region [67,68].

**Detailed computational head modeling.** cTBS field modeling will be conducted by generating realistic 3D head and coil geometries, solving for the E-field using the finite element method (FEM). T1w and T2w structural MRI (sMRI) and diffusion MRI (dMRI) will be combined to yield an individualized head model and white matter conductivity anisotropy. Tissue will be segmented into scalp, skull, CSF, gray matter, and white matter. Volumetric outputs will be entered into numerically optimized tetrahedral nodes using a Gmsh subroutine packaged in SimNIBS [69]. We will incorporate dMRI data to account for anisotropy effects of white matter. dMRI data will be pre-processed using the FDT toolkit in FSL and modeled using a tensor model; eigenvalues can be computed directly from the diffusion tensor eigenvalues and normalized using the geometric mean [70,71].

**Electric-Field calculations to optimize IPS cTBS.** The detailed head mesh from the anatomical data will be used to create E-field models to define the optimal cTBS coil orientation. The roll and pitch of the TMS coil handle will be defined perpendicular to the scalp. The yaw will be selected from 24 possible orientation vectors spaced at 15-degree increments. Separate E-field models will be conducted for each of the yaw vectors; E-field models will be used to generate E-field maps of the cortex given the corresponding stimulation parameters. E-field maps will be sampled at the stimulation target, and the yaw vector that induces the maximal E-field strength at the stimulation site will be selected for cTBS. We will simulate the E-field for coil placement over the motor hotspot.

**Neuronavigation.** Prior to the visits, target coordinates and orientation vectors will be generated from the fMRI data and e-field models, and loaded into Brainsight along with the reconstructed T1 image. Scalp and cortical surfaces will be generated from the T1. During the visits, the subject will be co-registered to the T1 using fiducial points at the Nasion and Tragi. Throughout the visits, cTBS pulses will be delivered to the target at the optimal orientation, and the accuracy of this targeted stimulation will be monitored and tracked by the Brainsight software. Overall stimulation accuracy will be used as a covariate in all statistical analyses.

### 2.7. Participant compensation

In line with our prior studies, participants will be compensated at an increasing rate to encourage continued participation. Participants will receive $40 for completion of the baseline evaluation, $50 for completion of Day 2, and $60 for completion of each subsequent visit (Days 4–35).

### 2.8. Outcomes

Self-reported and researcher-administered assessments will be recorded in the REDCap database (Table 1).

### 2.9. Primary outcome

***Startle magnitude.*** Electromyography (EMG) will be recorded from the left orbicularis oculi at 2000 Hz using a BIOPAC MP160 system with a FEMG100D smart amplifier [72]. Prior studies demonstrate that EMG startle recordings in the no/predictable/unpredictable threat paradigm show strong test–retest reliability in humans [73]. Startle is a highly reliable and valid measure of arousal, which is advantageous given our innovative design [74]. Responses will be sampled from 50 ms before to 120 ms after white noise onset. The raw signal will be bandpass filtered (30–300 Hz), rectified, and smoothed. Responses will be scored as the peak (max during the 20–120 ms post noise onset window) – the baseline (mean during -50 – 0 ms baseline; [28,75]). Raw scores will be standardized into *t*-scores [76,77]. Trials with excessive noise at baseline (2 SD above mean) will be outliers [75].

### 2.10. Secondary outcomes

***Negative outcome expectancy.*** Following trauma script generation during the baseline evaluation, participants will be asked for their expected outcome associated with listening to the recording of the trauma script. As described by Kindt [78], for some participants, the negative outcome expectancy will include fears of "falling apart", or not being able to tolerate distress, whereas for others, the expectancy might include fears of "losing control" or "going crazy." Once the idiographic negative outcome is identified, participants will be asked to provide a rating for each trial (trauma or neutral) to indicate their certainty about

the likelihood of the feared outcome on a scale from 0 ("certain no negative outcome") to 9 ("certain negative outcome") immediately before script onset.

***Subjective Units of Distress (SUDs).*** We will assess fear ratings using the prompt "On a scale from 0 to 10, how fearful does this recording make you?" rated on a scale from 0 (not at all) to 10 (very). Ratings will be collected prior to and after each script.

***Adverse events***. Participants will be asked whether they experienced a variety of adverse events, severity, relatedness of the symptom to the task (extinction training or cTBS) at the end of each study visit. We will track whether the symptom is expected or unexpected.

**Sample Size and Power Analysis.** We plan to recruit 120 participants assuming dropout of 10 % by Day 4 and a further 20 % dropout between Day 5 and 35. For each hypothesis, we will use an alpha level of 0.025. Based on prior research [28,59,76], we assume a within-participant correlation of 0.50 within each of the Day 4 and Day 34 startle responses, and a within-participant correlation of 0.4 between the two sessions. For our main effect of stimulation type (IPS cTBS vs. sham cTBS) and with these assumptions, our sample yields power of 80 % for an effect size of Cohen's $d = 0.40$. For our stimulation type x training type (extinction vs. neutral training) interaction, our sample yields 80 % power for a Cohen's $d = 0.52$.

### 2.11. Statistical analysis

Prior to conducting multivariate analyses, we will first examine descriptive statistics and test for potential demographic differences across variables. We do not expect to find differences associated with demographic factors; however, if we do find evidence of differences across our parameters of interest, we will include relevant demographic factors as covariates in subsequent analyses.

Using mixed-effects models, we will compare the active and sham cTBS groups on startle responses from the three blocks that follow cTBS pulses during Day 4 and Day 34 [77]. We will use startle from the initial pre-cTBS block of trials as a within-day baseline covariate to reduce error variance. Models will include a binary within-participant factor for order of training (neutral vs. trauma training), a categorical within-participant dose factor (cumulative 600, 1,200, and 1800 pulses), and a binary between-participant factor for stimulation type (IPS cTBS vs. sham cTBS). We expect that a compound symmetry structure (with parameter ρ1) within days and a compound symmetry structure (with parameter ρ2) between days will provide an adequate fit, but we will check other structures using AIC comparisons. We will perform our primary analyses on an intent-to-treat basis. Mixed-effects models will use all available data and yield valid inference when the missing data due to dropout after randomization are missing at random [78].

**Main effect of IPS cTBS, and interaction between IPS cTBS and Dose (assessment of optimal dosing).** cTBS main effect will estimate the effect of IPS cTBS vs. sham cTBS, pooling over training type (extinction vs. neutral) and dose (600, 1200, and 1800). We anticipate that the effect of stimulation type will be in the same direction at all dose levels, and we will evaluate the overall effect of IPS vs. sham cTBS. To assess how that effect differs across dose level, we will include the interaction between stimulation type (IPS cTBS vs. sham cTBS) and dose (cumulative 600, 1,200, and 1800 pulses). The inclusion of the interaction term will allow us to estimate the possibly different effects of cTBS type under the three different dose levels. The significance test for the overall interaction term will inform whether there are significantly different effects of stimulation type across the dose levels, and pairwise contrasts will identify where those differences occur. We anticipate that each of the 1200 and 1800 pulse doses will yield larger cTBS effects than the 600 pulse dose, and that there will not be a significant difference between the cTBS effect at the 1200 and 1800 pulse doses, which would suggest that 1200 may be an optimal dose for this population. Regardless of the significance of the overall interaction test, we will report estimated cTBS effects for the three dose levels, with associated standard errors, confidence intervals, and effect sizes, in addition to our estimated main effect of stimulation type.

**Interaction Between IPS cTBS, Dose, and Extinction Training (Startle Outcomes).** We will examine the interaction between training (extinction vs. neutral training) and stimulation type (IPS cTBS vs. sham cTBS), estimating the effects of cTBS type under trauma and neutral trials, and test the significance of the differences, while pooling at the level of dose of stimulation. We expect that IPS cTBS will reduce the magnitude of startle during the trauma vs. neutral trials compared to sham cTBS. To fully explore the interrelationships between stimulation type, dose, and training type, we will extend our models to include all two-way and the three-way interactions between factors. These analyses will address, for example, whether the interaction effect between stimulation and training type depends on dose.

**Further Analyses.** We will include baseline characteristics, including PTSD severity, global brain connectivity (GBC), etc., to explore whether these additional characteristics might be useful in tailoring of dose to individuals, by examining their interactions with the three design factors. We will calculate voxelwise GBC at baseline and sample this GBC map using a 5 mm sphere centered on the IPS stimulation site. This approach will result in a single GBC value representing the connectivity between the IPS hub and the rest of the brain to be entered as a predictor of dose analyses. We will also examine the effects of stimulation type, dose and training type on Negative Outcome Expectancy, and SUDs, using models described above.

**Startle Analyses During Retention (Days 5 & 35).** The outcome will be the startle responses obtained on Days 5 and 35. Analyses will be similar to those described for the training days, simplified by the absence of a dose factor. Models will include the average startle response after 1800 pulse trials of training as a covariate. We will assess the main effects of stimulation type (sham cTBS vs IPS cTBS) and training type (neutral vs trauma). We will include the stimulation type by training type interaction, estimating the effects of cTBS type under trauma and neutral trials, and test the significance of the differences.

**Further Analyses.** We will examine the effects of stimulation and training type on Negative Outcome Expectancy and SUDs, substituting this response for the Startle response in the analyses described above. To examine the effects of stimulation type on changes in neural activation of the IPS, we will compare the IPS and sham cTBS groups on resting state functional connectivity (rsFC) at Day 5 and 35, using a mixed effects model, with the day 2 measure of rsFC as a baseline covariate.

### 2.12. Missing data

Some participants will provide no responses for some outcomes and partial responses for others. Mixed-effects models will use all available data and yield valid inference when the missing data due to dropout after randomization are missing at random. We will use an inverse probability weighting approach to assess sensitivity to this assumption; and will also estimate pattern mixture models. In reporting our results, we will describe missing data patterns and describe the conclusions of these sensitivity analyses. Some participants will provide no responses for some outcomes and partial responses for others. Mixed-effects models will use all available data and yield valid inference when the missing data due to dropout after randomization are missing at random [78]. We will use an inverse probability weighting approach to assess sensitivity to this assumption; and will also estimate pattern mixture models. In reporting our results, we will describe missing data patterns and describe the conclusions of these sensitivity analyses.

## 3. Ethics approval

Ethical considerations of human participants outlined in this protocol are approved by the IRB of the University of Pennsylvania (Protocol Number: 849571).

## 4. Results

Preliminary study activities such as IRB approval, training of study personnel, and development of study procedures began in January 2024. Recruitment began in April 2024; we anticipate completing recruitment by April 2028 (Fig. 4). Study results will be disseminated in 2029.

## 5. Discussion

### 5.1. Principal contributions to the field

This experimental study will serve as a mechanistic probe to evaluate whether cTBS can augment extinction training. Our design will test the effect of active IPS stimulation relative to sham IPS stimulation, probing the effect of extinction training relative to control training, and the addition of IPS stimulation to extinction training. We will evaluate the optimal dose of IPS cTBS as well as conduct an exploratory analysis to evaluate the neural underpinnings of IPS cTBS as it relates to extinction training and subsequent retention of extinction learning. We selected IPS cTBS, in contrast to prefrontal TMS, given the status of IPS as a connectivity "hub" mediating arousal [79] and its role in reducing arousal symptoms. All ongoing and completed TMS studies for PTSD have targeted the prefrontal cortex, which is known to reduce depression [80] and re-experiencing symptoms [37,81], with no clear-cut evidence for a reduction in arousal symptoms. This integrated protocol offers a novel therapeutic option to target **arousal** among patients with PTSD and to evaluate the additive or synergistic effects of IPS cTBS and extinction training on arousal symptoms. Upon completion of this project, we expect to have tested the mechanism underlying a procedure for reducing PTSD-related arousal through integrating extinction training with IPS cTBS. Our findings will strengthen the neurobiological basis of augmenting extinction training with IPS cTBS.

## 6. Limitations

The findings from this study will only pertain to patients with PTSD; however, anticipate that these findings will be of relevance to other disorders that demonstrate alterations in the arousal system, including other anxiety-related disorders. Furthermore, our study design will not allow us to determine the number of training sessions that will be necessary for symptom reduction. We will also be limited in our ability to discern whether results are specific to trauma-related cues or general effects of extinction learning. The findings from this study will pave the way for subsequent clinical trials to clarify these limitations.

### 6.1. Comparison with prior work

Prior neuromodulation trials for PTSD have targeted the prefrontal cortex using rTMS, which has demonstrated limited effects on arousal symptoms. However, to date, no research has explored IPS neuromodulation in patients with PTSD. Fluctuations in arousal with treatment are associated with differences in neural connectivity compared to other PTSD symptom clusters; however, psychopharmacological efforts to modulate arousal during extinction learning using medications have yielded mixed [22–25]. Given that the IPS serves as a critical region underlying the regulation of arousal and anxiety expression, neurostimulation of this region may be a novel target for modulating arousal during extinction training.

## 7. Conclusions

This novel research will be the first study to examine the extent to which IPS cTBS attenuates arousal, as indicated by a startle eyeblink response ("startle"), relative to sham cTBS among individuals with PTSD.

## CRediT authorship contribution statement

**Sonalee A. Joshi:** Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Data curation. **Tao Lin:** Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Data curation. **Nicholas L. Balderston:** Writing – review & editing, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Kevin G. Lynch:** Writing – review & editing, Software, Resources, Methodology, Formal analysis, Conceptualization. **Mingcong Tang:** Writing – review & editing, Project administration, Data curation. **Milan Patel:** Writing – review & editing, Project administration, Data curation. **Ivy Sun:** Writing – review & editing, Project administration, Data curation. **Barbara Fureman:** Writing – review & editing, Project administration, Data curation. **Desmond J. Oathes:** Writing – review & editing, Supervision, Investigation, Funding acquisition, Conceptualization. **David F. Gregory:** Writing – review & editing, Visualization, Validation, Project administration, Methodology, Data curation. **Yvette I. Sheline:** Writing – review & editing, Validation, Supervision, Resources, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Lily A. Brown:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources,

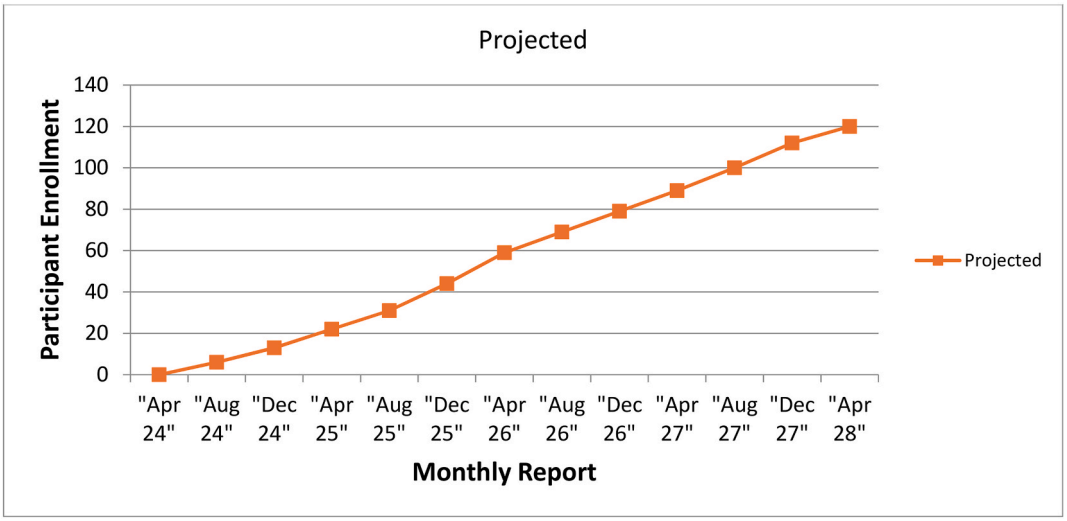


**Fig. 4.** Projected participant enrollment.

Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

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## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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None.

## Data availability

No data was used for the research described in the article.

## References

[1] D.G. Kilpatrick, National estimates of exposure to traumatic events and PTSD prevalence using DSM-IV and DSM-5 criteria 26 (5) (2013) 537–547.
[2] P.-F. Rousseau, Fear extinction learning improvement in PTSD after EMDR therapy: an fMRI study, Eur. J. Psychotraumatol. 10 (1) (2019) 1568132, https://doi.org/10.1080/20008198.2019.1568132.
[3] M.W. Lewis, C.A. Webb, M. Kuhn, E. Akman, S.A. Jobson, I.M. Rosso, Predicting fear extinction in posttraumatic stress disorder, Brain Sci. 13 (8) (July 2023) 1131, https://doi.org/10.3390/brainsci13081131.
[4] S. Maren, A. Holmes, Stress and fear extinction, Neuropsychopharmacology 41 (1) (Jan. 2016) 58–79, https://doi.org/10.1038/npp.2015.180.
[5] P.A. Resick, M.K. Schnicke, Cognitive Processing Therapy for Rape Victims: a Treatment Manual, Sage Publications, Newbury Park, CA, 1993.
[6] S.P. Orr, De novo conditioning in trauma-exposed individuals with and without posttraumatic stress disorder, J. Abnorm. Psychol. 109 (2) (2000) 290–298, https://doi.org/10.1037/0021-843X.109.2.290.
[7] S. Lissek, Classical fear conditioning in the anxiety disorders: a meta-analysis, Behav. Res. Ther. 43 (11) (2005) 1391–1424, https://doi.org/10.1016/j.brat.2004.10.007.
[8] R.K. Pitman, Psychophysiologic assessment of posttraumatic stress disorder imagery in Vietnam combat veterans, Arch. Gen. Psychiatry 44 (11) (1987) 970–975, https://doi.org/10.1001/archpsyc.1987.01800230050009.
[9] S.P. Orr, Psychophysiologic assessment of women with posttraumatic stress disorder resulting from childhood sexual abuse, J. Consult. Clin. Psychol. 66 (6) (1998) 906–913, https://doi.org/10.1037/0022-006X.66.6.906.
[10] A.Y. Shalev, Psychophysiologic assessment of mental imagery of stressful events in Israeli civilian posttraumatic stress disorder patients, Compr. Psychiatry 38 (5) (1997) 269–273, https://doi.org/10.1016/S0010-440X(97)90059-6.
[11] E.B. Blanchard, Psychophysiology of posttraumatic stress disorder related to motor vehicle accidents: replication and extension, J. Consult. Clin. Psychol. 64 (4) (1996) 742–751, https://doi.org/10.1037/0022-006X.64.4.742.
[12] J.A. Anderson, Arousal and the inverted-U hypothesis: a critique of Neiss's 'reconceptualizing arousal, Psychol. Bull. 107 (1990) 96–100, https://doi.org/10.1037/0033-2909.107.1.96.
[13] C.C. McCormack, R.J. Mennies, J.S. Silk, L.B. Stone, How anxious is too anxious? State and trait physiological arousal predict anxious youth's treatment response to brief cognitive behavioral therapy, BMC Psychol. 8 (1) (2020), https://doi.org/10.1186/s40359-020-00415-3.
[14] E.B. Foa, M.J. Kozak, Emotional processing of fear: exposure to corrective information, Psychol. Bull. 99 (1986) 20–35, https://doi.org/10.1037/0033-2909.99.1.20.
[15] R.A. Bryant, Amygdala and ventral anterior cingulate activation predicts treatment response to cognitive behaviour therapy for post-traumatic stress disorder, Psychol. Med. 38 (4) (2008) 555–561, https://doi.org/10.1017/S0033291707002231.
[16] S. Rauch, E. Foa, Emotional processing theory (EPT) and exposure therapy for PTSD, J. Contemp. Psychother. 36 (2) (2006) 61, https://doi.org/10.1007/s10879-006-9008-y.
[17] S.R. Miles, Hyperarousal symptoms linger after successful PTSD treatment in active duty military, Psychol. Trauma: Theory, Research, Practice, Policy (2025).
[18] L.A. Brown, J.D. Clapp, J.J. Kemp, The pattern of symptom change during prolonged exposure therapy and present-centered therapy for PTSD in active duty military personnel, Psychol. Med. 49 (12) (2019) 1980–1989, https://doi.org/10.1017/S0033291718002714.
[19] M.A. Schottenbauer, C.R. Glass, D.B. Arnkoff, V. Tendick, S.H. Gray, Nonresponse and dropout rates in outcome studies on PTSD, Review and Methodological Considerations. Psychiatry: Interpersonal and Biological Processes 71 (2) (2008) 134–168, https://doi.org/10.1521/psyc.2008.71.2.134.
[20] E.S. Stevens, K.J. Bourassa, A.M. Norr, G.M. Reger, Posttraumatic stress disorder symptom cluster structure in prolonged exposure therapy and virtual reality exposure, J. Trauma Stress 4 (2) (2020) 287–297.
[21] E.S. Stevens, K.J. Bourassa, A.M. Norr, G.M. Reger, Posttraumatic stress disorder symptom cluster structure in prolonged exposure therapy and virtual reality exposure, J. Trauma Stress 34 (2) (2021) 287–297, https://doi.org/10.1002/jts.22602.
[22] D. Mueller, S.P. Cahill, Noradrenergic modulation of extinction learning and exposure therapy, Behav. Brain Res. 208 (1) (2010) 1–11, https://doi.org/10.1016/j.bbr.2009.11.025.
[23] M. Ouyang, S.A. Thomas, A requirement for memory retrieval during and after long-term extinction learning, Proc. Natl. Acad. Sci. U. S. A. 102 (26) (2005) 9347–9352, https://doi.org/10.1073/pnas.0502315102.
[24] C. Grillon, J. Cordova, C.A. Morgan, D.S. Charney, M. Davis, Effects of the beta-blocker propranolol on cued and contextual fear conditioning in humans, Psychopharmacology (Berl 175 (3) (2004) 342–352, https://doi.org/10.1007/s00213-004-1819-5.
[25] S.B. Morissette, D.A. Spiegel, D.H. Barlow, Combining exposure and pharmacotherapy in the treatment of social anxiety disorder: a preliminary study of state dependent learning, J. Psychopathol. Behav. Assess. 30 (3) (2008) 211–219, https://doi.org/10.1007/s10862-007-9061-1.
[26] R. Famularo, R. Kinscherff, T. Fenton, Propranolol treatment for childhood posttraumatic stress disorder, acute type. A pilot study, Am. J. Dis. Child. 142 (11) (1988) 1244–1247, https://doi.org/10.1001/archpedi.1988.02150110122036.
[27] P.W. Tuerk, B.C. Wangelin, M.B. Powers, Augmenting treatment efficiency in exposure therapy for PTSD: a randomized double-blind placebo-controlled trial of yohimbine HCl, Cogn. Behav. Ther. 47 (5) (2018) 351–371, https://doi.org/10.1080/16506073.2018.1432679.
[28] N.L. Balderston, E. Hale, A. Hsiung, Threat of shock increases excitability and connectivity of the intraparietal sulcus, Neuroscience 6 (6) (2017).
[29] N.L. Balderston, E.M. Beydler, M. Goodwin, Low-frequency parietal repetitive transcranial magnetic stimulation reduces fear and anxiety, Transl. Psychiatry 10 (1) (2020), https://doi.org/10.1038/s41398-020-0751-8.
[30] D.R. Bach, Rising sound intensity: an intrinsic warning cue activating the amygdala, Cerebr. Cortex 18 (1) (2007) 145–150, https://doi.org/10.1093/cercor/bhm040.
[31] Y.-H. Jung, Altered Amygdala Resting-State Functional Connectivity and Hemispheric Asymmetry in Patients with Social Anxiety Disorder, vol. 9, 2018.
[32] T. Yan, Q. Xie, Z. Zheng, K. Zou, L. Wang, Different frequency repetitive transcranial magnetic stimulation (rTMS) for posttraumatic stress disorder (PTSD): a systematic review and meta-analysis, J. Psychiatr. Res. 89 (June 2017) 125–135, https://doi.org/10.1016/j.jpsychires.2017.02.021.
[33] L. Brown, L.K. White, W. Makhoul, M. Teferi, Y.I. Sheline, N.L. Balderston, Role of the intraparietal sulcus (IPS) in anxiety and cognition: opportunities for intervention for anxiety-related disorders, Int. J. Clin. Health Psychol. 23 (4) (Oct. 2023) 100385, https://doi.org/10.1016/j.ijchp.2023.100385.
[34] X. Zhu, B. Suarez-Jimenez, A. Lazarov, Exposure-based therapy changes amygdala and hippocampus resting-state functional connectivity in patients with posttraumatic stress disorder, Depress. Anxiety 35 (10) (2018) 974–984, https://doi.org/10.1002/da.22816.
[35] W. Heller, Neuropsychological mechanisms of individual differences in emotion, personality, and arousal, Neuropsychology 7 (4) (1993) 476–489, https://doi.org/10.1037/0894-4105.7.4.476.
[36] E.A. Osuch, Repetitive TMS combined with exposure therapy for PTSD: a preliminary study, J. Anxiety Disord. 23 (1) (2009) 54–59, https://doi.org/10.1016/j.janxdis.2008.03.015.
[37] M. Isserles, Effectiveness of deep transcranial magnetic stimulation combined with a brief exposure procedure in post-traumatic stress disorder – a pilot study, Brain Stimul. 6 (3) (2013) 377–383, https://doi.org/10.1016/j.brs.2012.07.008.
[38] S.M. Dudek, M.F. Bear, Homosynaptic long-term depression in area CA1 of hippocampus and effects of N-methyl-D-aspartate receptor blockade, Proc. Natl. Acad. Sci. U. S. A 89 (10) (May 1992) 4363, https://doi.org/10.1073/pnas.89.10.4363.
[39] S.M. Dudek, M.F. Bear, Bidirectional long-term modification of synaptic effectiveness in the adult and immature hippocampus, J. Neurosci. 13 (7) (July 1993) 2910, https://doi.org/10.1523/JNEUROSCI.13-07-02910, 1993.
[40] Y.-Z. Huang, M.J. Edwards, E. Rounis, K.P. Bhatia, J.C. Rothwell, Theta burst stimulation of the human motor cortex, Neuron 45 (2) (2005) 201–206, https://doi.org/10.1016/j.neuron.2004.12.033.
[41] Y.-Z. Huang, J.C. Rothwell, R.-S. Chen, C.-S. Lu, W.-L. Chuang, The theoretical model of theta burst form of repetitive transcranial magnetic stimulation, Clin. Neurophysiol. : official journal of the International Federation of Clinical Neurophysiology 122 (5) (May 2011) 1011, https://doi.org/10.1016/j.clinph.2010.08.016.
[42] Y.-Z. Huang, et al., The effect of continuous theta burst stimulation over premotor cortex on circuits in primary motor cortex and spinal cord, Clin. Neurophysiol. 120 (4) (Apr. 2009) 796–801, https://doi.org/10.1016/j.clinph.2009.01.003.
[43] C. Wendelken, Maintaining structured information: an investigation into functions of parietal and lateral prefrontal cortices, Neuropsychologia 46 (2) (2008) 665–678, https://doi.org/10.1016/j.neuropsychologia.2007.09.015.
[44] D. Alnæs, Functional connectivity indicates differential roles for the intraparietal sulcus and the superior parietal lobule in multiple object tracking, Neuroimage 123 (2015) 129–137, https://doi.org/10.1016/j.neuroimage.2015.08.029.

[45] O.L. Gamboa, A. Antal, B. Laczo, V. Moliadze, M.A. Nitsche, W. Paulus, Impact of repetitive theta burst stimulation on motor cortex excitability, Brain Stimul. 4 (3) (2011) 145–151, https://doi.org/10.1016/j.brs.2010.09.008.
[46] R. Gentner, K. Wankerl, C. Reinsberger, D. Zeller, J. Classen, Depression of human corticospinal excitability induced by magnetic theta-burst stimulation: evidence of rapid polarity-reversing metaplasticity, Cerebr. Cortex 18 (9) (2008) 2046–2053, https://doi.org/10.1093/cercor/bhm239.
[47] A. Jannati, P.J. Fried, G. Block, L.M. Oberman, A. Rotenberg, A. Pascual-Leone, Test-retest reliability of the effects of continuous theta-burst stimulation, Front. Neurosci. 13 (447) (2019).
[48] C.-T. Li, M.-H. Chen, C.-H. Juan, Efficacy of prefrontal theta-burst stimulation in refractory depression: a randomized sham-controlled study, Brain 137 (7) (2014) 2088–2098, https://doi.org/10.1093/brain/awu109.
[49] F. Rachid, Safety and efficacy of theta-burst stimulation in the treatment of psychiatric disorders: a review of the literature, J. Nerv. Ment. Dis. 205 (11) (2017) 823–839, https://doi.org/10.1097/NMD.0000000000000742.
[50] E.J. Cole, K.H. Stimpson, B.S. Bentzley, Stanford accelerated intelligent neuromodulation therapy for treatment-resistant depression, Am. J. Psychiatr. 177 (8) (2020) 716–726, https://doi.org/10.1176/appi.ajp.2019.19070720.
[51] F. Rachid, Accelerated transcranial magnetic stimulation for the treatment of patients with depression: a review, Asian J Psychiatr 40 (2019) 71–75, https://doi.org/10.1016/j.ajp.2019.02.003.
[52] F.W. Weathers, The clinician-administered PTSD scale for DSM-5 (CAPS-5): Development and initial psychometric evaluation in military veterans, Psychol. Assess. 30 (3) (2018) 383–395, https://doi.org/10.1037/pas0000486.
[53] L.E. Pincus, Consultation and professional development within the prolonged exposure initiative, J. Community Psychol. (2022), https://doi.org/10.1002/jcop.22800.
[54] L.E. Pincus, Trauma exposure and PTSD in Philadelphia community mental health, Community Ment. Health J. 58 (3) (2022) 547–552, https://doi.org/10.1007/s10597-021-00853-2.
[55] F.W. Weathers, C.A. Byrne, B.P. Marx, P.P. Schnurr, T.M. Keane, The Clinician-Administered PTSD Scale for DSM-5, Revised (CAPS-5-R)–Past Month–Initial Interview Version, 2022.
[56] M. B. First, "Structured clinical interview for the DSM (SCID," in The Encyclopedia of Clinical Psychology.1-6.
[57] K. Posner, The columbia-suicide severity rating scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults, Am. J. Psychiatr. 168 (12) (2011) 1266–1277, https://doi.org/10.1176/appi.ajp.2011.10111704.
[58] R.K. Pitman, Psychophysiologic assessment of posttraumatic stress disorder imagery in Vietnam combat veterans, Arch. Gen. Psychiatry 44 (11) (Nov. 1987) 970, https://doi.org/10.1001/archpsyc.1987.01800230050009.
[59] L.A. Brown, Linguistic processing and script-driven imagery for trauma exposure: a proof of concept pilot trial, J. Anxiety Disord. 57 (2018) 16–23, https://doi.org/10.1016/j.janxdis.2018.05.010.
[60] J.J. Borckardt, Z. Nahas, J. Koola, M.S. George, Estimating resting motor thresholds in transcranial magnetic stimulation research and practice: a computer simulation evaluation of best methods, J. ECT 22 (3) (2006) 169–175, https://doi.org/10.1097/01.yct.0000235923.52741.72.
[61] R.F.H. Cash, L. Cocchi, J. Lv, P.B. Fitzgerald, A. Zalesky, Functional magnetic resonance imaging–guided personalization of transcranial magnetic stimulation treatment for depression, JAMA Psychiatry 78 (3) (2020) 337–339.
[62] P.P. Thakral, K.P. Madore, S.E. Kalinowski, D.L. Schacter, Modulation of hippocampal brain networks produces changes in episodic simulation and divergent thinking, Proc. Natl. Acad. Sci. 117 (23) (2020), https://doi.org/10.1073/pnas.2003535117.
[63] N.E. Adleman, et al., A developmental fMRI study of the stroop color-word task, Neuroimage 16 (1) (May 2002) 61–75, https://doi.org/10.1006/nimg.2001.1046.
[64] J.R. Stroop, Studies of interference in serial verbal reactions, J. Exp. Psychol. 18 (6) (1935) 643–662, https://doi.org/10.1037/h0054651.
[65] R.W. Cox, AFNI: software for analysis and visualization of functional magnetic resonance neuroimages, Comput. Biomed. Res. 29 (3) (June 1996) 162–173, https://doi.org/10.1006/cbmr.1996.0014.
[66] P. Kundu, S.J. Inati, J.W. Evans, W.-M. Luh, P.A. Bandettini, Differentiating BOLD and Non-BOLD signals in fMRI time series using multi-echo EPI, Neuroimage 60 (3) (Dec. 2011) 1759, https://doi.org/10.1016/j.neuroimage.2011.12.028.
[67] N.L. Balderston, et al., Low-frequency parietal repetitive transcranial magnetic stimulation reduces fear and anxiety, Transl. Psychiatry 10 (1) (Feb. 2020) 68, https://doi.org/10.1038/s41398-020-0751-8.
[68] N.L. Balderston, et al., A generalized workflow for conducting electric field–optimized, fMRI-guided, transcranial magnetic stimulation, Nat. Protoc. 15 (11) (Nov. 2020) 3595–3614, https://doi.org/10.1038/s41596-020-0387-4.
[69] A. Thielscher, A. Antunes, G.B. Saturnino, Field modeling for transcranial magnetic stimulation: a useful tool to understand the physiological effects of TMS? Conf Proc IEEE Eng Med Biol Soc 2015 (2015) 222–225.
[70] J. Haueisen, C. Ramon, M. Eiselt, H. Brauer, H. Nowak, Influence of tissue resistivities on neuromagnetic fields and electric potentials studied with a finite element model of the head, IEEE Trans. Biomed. Eng. 44 (8) (1997) 727–735, https://doi.org/10.1109/10.605429.
[71] D. Gullmar, J. Haueisen, J. Reichenbach, Influence of anisotropic electrical conductivity in white matter tissue on the EEG/MEG forward and inverse solution. A high-resolution whole head simulation study, Neuroimage 51 (1) (2010) 145–163, https://doi.org/10.1016/j.neuroimage.2010.02.014.
[72] N.L. Balderston, Set of scripts to analyze EMG startle response [Online]. Available: https://github.com/balders2/analyze_startle, 2022.
[73] L. Lieberman, S.M. Gorka, J.A. Digangi, A. Frederick, K.L. Phan, Progress in Neuropsychopharmacology & biological psychiatry impact of posttraumatic stress symptom dimensions on amygdala reactivity to emotional faces, Progress in Neuropsychopharmacology & Biological Psychiatry 79 (May) (2017) 401–407, https://doi.org/10.1016/j.pnpbp.2017.07.021.
[74] J. Wendt, M. Kuhn, A.O. Hamm, T.B. Lonsdorf, Recent advances in studying brain-behavior interactions using functional imaging: the primary startle response pathway and its affective modulation in humans, Psychophysiology 60 (12) (2023) e14364, https://doi.org/10.1111/psyp.14364.
[75] T.D. Blumenthal, Committee report: guidelines for human startle eyeblink electromyographic studies 42 (1) (2005) 1–15.
[76] J.T. Kaye, Psychometric properties of startle and corrugator response in NPU, affective picture viewing, and resting state tasks, Psychophysiology 53 (8) (2016) 1241–1255, https://doi.org/10.1111/psyp.12663.
[77] A. Schmitz, C. Grillon, Assessing fear and anxiety in humans using the threat of predictable and unpredictable aversive events (the NPU-Threat test, Nat. Protoc. 7 (3) (2012) 527–532, https://doi.org/10.1038/nprot.2012.001.
[78] M. Kindt, The surprising subtleties of changing fear memory: a challenge for translational science, Phil. Trans. Biol. Sci. 373 (1742) (2018), https://doi.org/10.1098/rstb.2017.0033.
[79] N.L. Balderston, M. Goodwin, A. Beale, M. Ernst, C. Grillon, Threat of shock influences parietal bold responses during a visual short-term memory task, Society for Neuroscience (2019).
[80] K.R. Connolly, A. Helmer, M.A. Cristancho, P. Cristancho, J.P. O'Reardon, Effectiveness of transcranial magnetic stimulation in clinical practice post-FDA approval in the United States: results observed with the first 100 consecutive cases of depression at an academic medical center, J. Clin. Psychiatry 73 (4) (2012) e567–e573, https://doi.org/10.4088/JCP.11m07413.
[81] D.H. Nam, C.U. Pae, C.J.H. Low-frequency, Repetitive transcranial magnetic stimulation for the treatment of patients with posttraumatic stress disorder: a double-blind, sham-Controlled study, Clin Psychopharmacol Neurosci 11 (2) (2013) 96–102, https://doi.org/10.9758/cpn.2013.11.2.96.

## Abbreviations

***CAPS-5:*** Clinician Administered PTSD Scale- 5
***CAPS-5R:*** Clinician Administered PTSD Scale- 5 Revised
***C-SSRS:*** Columbia–Suicide Severity Rating Scale
***cTBS:*** continuous theta burst stimulation
***EMG:*** Electromyography
***GBC:*** global brain connectivity
***IPS:*** intraparietal sulcus
***IRB:*** institutional review board
***PEST:*** parameter estimation by sequential testing
***PFC:*** prefrontal cortex
***rsFC:*** resting state functional connectivity
***rTMS:*** repetitive transcranial magnetic stimulation
***SCID-5:*** The Structured Clinical Interview for DSM-5
***SUDs:*** Subjective Units of Distress