Effect of Transcranial Magnetic Stimulation (TMS) on PTSD Neuroimaging and Psychophysiological Biomarkers

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PROTOCOL TITLE: Effect of Transcranial Magnetic Stimulation (TMS) on PTSD Neuroimaging and Psychophysiological Biomarkers

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Tanja Jovanovic, PhD, Professor, Wayne State University, Department of Psychiatry and Behavioral Neurosciences. No human subjects research will occur at Wayne State University.

Karin Machluf, PhD, Assistant Professor, Georgia State University, Department of Psychology. No human subjects research will occur at Georgia State University. Emory will be reviewing for Dr. Machluf.

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REVISION HISTORY

Revision #	Version Date	Summary of Changes
1	1.1	Clarification of Internal Audit for Data completeness and safety concerns
2	1.2	Addition of a second MRI review by qualified research scientist

3	1.3	Changing the time between treatments from 30 minutes to 10 minutes Adding PCL-5 to the day of the DA. Participant will be excluded if participant improved >10 points on the PCL-5 Adding question about alcohol and drug use: Before each TMS session the participant is asked if they have had any alcohol, drug and medication use in the past 24 hours. CAPS-5 added at 3 months CD-Risc added at pre-intervention assessment Addition of DTI and removal of Fear Extinction task (section 6.4) Psychotropic medication, per DSMB needs to be specified. We will exclude for psychotropic medication use (specifically: antidepressants, antipsychotics, benzodiazepines and anticonvulsants) at time of enrollment and participants cannot start taking any of these psychotropic medications during the course of the study. Addition of Insomnia Severity Index before treatment (together with CD-RISC/BDI) and after (again with BDI etc) and also during 3mo assessment: Addition of pregnancy test prior to Motor Threshold Testing
4	1.4	PCL-5 removed from visit 1 and 6 BDI added at the same time as PCL-5 at visits 5 and 10 Take out exclusion for 10-point improvement in pre-treatment PCL-5 score
5	1.5	Adding optional EEG sub-study
6	1.6	Change following inclusion criteria: broaden PTSD diagnosis remove past suicide attempts as exclusion

		exclusion for lifetime diagnosis of psychotic disorder or bipolar I disorder assessed during diagnostic interview Removing fifth EEG recording from TMS treatment. Adding post-proceedure EEG recording for pre and post treatment EEG recording days.
7	1.7	Recruitment Methods 13.4 changed from no materials to fliers posted in the community and social media advertisements will be used for recruitment. Added social media management plan.
8	1.8	Added Emory Multimodal Learning Test
9	1.9	Added GSU faculty Karin Machluf to study team.

Table of Contents

1.0 Study Summary

Study Title	Effect of TMS on PTSD Neuroimaging and Psychophysiological Biomarkers
Study Design	Randomized Controlled Trial
Primary Objective	Examine effect of TMS on PTSD biomarkers
Secondary Objective(s)	Examine effect of TMS on PTSD hyperarousal symptoms
Research Intervention(s)/Interactions	Transcranial Magnetic Stimulation (TMS). Two weeks, 5 days per week, two treatments per day, 30 minutes each with 10-minute break
Study Population	PTSD patients
Sample Size	Final sample of N=60 (N=30 active TMS, N=30 sham TMS)
Study Duration for individual participants	3 months
Study Specific Abbreviations/ Definitions	TMS, transcranial magnetic stimulation PTSD, posttraumatic stress disorder MRI, magnetic resonance imaging RS, resting state FC, functional connectivity FPS, fear-potentiated startle
Funding Source (if any)	National Institute of Mental Health (NIMH)

2.0 Objectives

2.1 Specific Aims:

Specific Aim 1: Examine the effect of TMS on PTSD neuroimaging biomarkers.

Specific Aim 2: Examine the effect of TMS on PTSD psychophysiology biomarkers.

Specific Aim 3: Assess the effect of TMS on PTSD hyperarousal symptoms and physiology.

2.2 Hypotheses to be tested:

For Specific Aim 1, we will test three hypotheses: H1a: TMS vs. sham will increase inhibition-related ventromedial (vm)PFC and hippocampal activation and will decrease amygdala activation during fear conditioning and inhibition. H1b: TMS vs. sham will increase vmPFC-amygdala and DLPFC-amygdala FC post-treatment. H1c: subjects whose DLPFC TMS target, as

defined with structural neuronavigation, was (more) functionally connected with the amygdala will show more effect of TMS on H1a and H1b.

For Specific Aim 2, we will test three hypotheses: H2a: TMS vs. sham will reduce FPS responses to safety cues. H2b: TMS vs. sham will reduce SCR to trauma cues post-treatment. H2c: similar to H1c, those subjects with increased FC between the DLPFC TMS target and amygdala will show more effect of TMS on H2a and H2b.

For Specific Aim 3, we test two competing hypotheses: H3a: Direct TMS effect – directly decreasing amygdala hyperactivation results in reduced hyperarousal immediately post-treatment; H3b: Indirect TMS effect – improved PFC-amygdala FC leads to reduction in hyperarousal from ongoing top-down regulation, but not observed until 3 months post-treatment

3.0 Background

3.1 Posttraumatic stress disorder (PTSD) is a debilitating psychiatric disorder resulting in significant emotional and financial burden along with a high risk for suicide (Kessler et al., 1995a; Kessler, 2000). Even though the first-line trauma-focused psychotherapeutic and pharmacological treatments for PTSD are efficacious for some patients (Bradley et al., 2005), rates of refusal or drop-out are high and many do not benefit from time-intensive and cognitively demanding therapies or medications. Additionally, development of novel treatments is hampered by a lack of understanding of neural mechanisms underlying recovery from PTSD.

The neurocircuitry underlying fear processing has been robustly implicated in PTSD. Patients demonstrate heightened fear-potentiated startle (FPS) responses to danger and safety cues (Jovanovic et al., 2012), and increased skin conductance responses (SCR) to trauma reminders (Hinrichs et al., 2017). Neuroimaging studies demonstrate decreased prefrontal regulation of an overactive amygdala (Stevens et al., 2013) and impaired hippocampal-dependent context processing (van Rooij et al., 2018). Treatment studies suggest a neurobiological profile related to PTSD treatment non-response, including an overactive amygdala (van Rooij et al., 2016) and reduced activation of frontal inhibitory networks (van Rooij et al., 2015).

There is significant interest in using focal neuromodulation, such as transcranial magnetic stimulation (TMS) to induce functional brain changes as a treatment for psychiatric disorders; however, the mechanisms underlying the therapeutic effects of TMS remain unclear.

3.2 TMS, an FDA-approved noninvasive treatment for pharmaco-resistant major depressive disorder (MDD), has shown mixed treatment efficacy in both MDD (Mantovani et al., 2012; O'Reardon et al., 2007) and PTSD populations (Nam et al., 2013; Watts et al 2012). A study in healthy

volunteers demonstrated that 1Hz TMS to the rDLPFC reduced amygdala reactivity to threatening stimuli (Beaken et al., 2010). Some recent studies in MDD patients have also begun neurobiological assessments of TMS. Liston et al (2014) demonstrated that TMS provokes changes distal to the stimulation site and modifies impaired functional brain connections within the default mode network. Philip et al. (2018) used 5Hz TMS to the left DLPFC and observed meaningful clinical improvement in PTSD and depression symptoms after 3 weeks in 36% and 33% of patients, respectively. Moreover, increased amygdala-mPFC FC was found to predict TMS treatment response. A negative correlation between clinical improvement and change in right sgACC-left DLPFC and left anterior hippocampus-right dACC FC was observed (Philip et al., 2018).

3.3 More than half of individuals in the United States experience at least one traumatic event in their lifetime (Kessler et al., 1995a; Resnick et al., 1994). In the general population, the lifetime prevalence of post-traumatic stress disorder (PTSD) has been estimated to be 5-10% (Kessler et al., 1995b), but rates are as high as 23% in war veterans (Fulton et al., 2015) and 30-50% among civilians living in inner-city areas with high violence (Gillespie et al., 2009). Even though the first-line trauma-focused psychotherapeutic treatments for PTSD are highly efficacious for patients who are able to engage in therapy (Bradley et al., 2005), there are a number of limitations with these treatments related to low tolerability for patients with chronic trauma exposure, high rates of drop out, and non-response despite engagement (Orsillo & Batten, 2005; Resick et al., 2002). Trauma-focused therapies often involve significant writing and worksheet-based homework which could be a barrier for people with low education and/or literacy (Davis et al., 2008). Limited access to behavioral health care or stigma against such treatment reduces the chance that patients seek care or are willing to engage in direct exposure-based trauma treatment (Davis et al., 2008).

Thus, the development of alternative treatment approaches to PTSD is warranted. There is significant interest in using focal neuromodulation such as Transcranial Magnetic Stimulation (TMS) to induce functional brain changes as a potential treatment for psychiatric disorders. TMS is a noninvasive treatment that uses magnetic fields to induce a small electric current in specific brain regions. The mechanism of TMS for PTSD is largely unknown, hindering advancement of this treatment. This study will significantly contribute to the advancement of treatment approaches for PTSD by: (1) determining if 1Hz TMS to right DLPFC improves PTSD intermediate phenotypes; (2) suggesting novel brain modulation targets for future studies; (3) providing preliminary data for future work examining individual differences in treatment response; and (4) advancing

understanding of the neurobiology of PTSD treatment response using TMS as a probe.

4.0 Study Endpoints *

4.1 Primary study endpoints: the effect of TMS vs sham on neuroimaging and psychophysiological biomarkers.

Neuroimaging biomarkers: pre- and post-treatment neuroimaging data will be collected on a 3T Siemens Trio MRI scanner. TMS vs sham is expected to increase inhibition-related activation in the ventromedial prefrontal cortex (vmPFC) and hippocampus, decrease amygdala activation during fear conditioning and inhibition, and increase vmPFC-amygdala and DLPFC-amygdala functional connectivity (FC) post- compared to pre-treatment.

Psychophysiological biomarkers: pre- and post-treatment psychophysiological data will be collected in a startle booth as well as using a mobile skin conductance device. TMS vs sham is expected to reduce the general fear-potentiated startle (FPS) response to both danger and safety cues, increase discrimination between danger and safety, and reduce SCR to trauma cues post- compared to pre-treatment.

Secondary study endpoints: PTSD hyperarousal symptoms. Hyperarousal symptoms will be assessed using the PTSD checklist for DSM-5 and include hypervigilance, sleep problems, difficulty concentrating, self-destructive behavior and irritability.

4.2 We do not expect any adverse events, because TMS has been safely administered in numerous studies and clinical settings. The primary safety endpoint is safe administration of TMS in the PTSD study population by tracking adverse events occurring during the study.

5.0 Study Intervention/Investigational Agent

1.1 Transcranial Magnetic Stimulation (TMS) is a noninvasive treatment that uses magnetic fields to induce a small electric current in specific brain regions. It is an FDA-approved treatment for pharmaco-resistant major depressive disorder (MDD).

5.1 The TMS machine is located in the Emory Brain Health Center (BHC), 12 Executive Park, Atlanta GA, 30329, in a room on the first floor that is locked and only accessible by Dr. McDonald (Medical Director of the Electroconvulsive and Neuromodulation Therapy Services), the TMS technician, the PI, and Psychiatric Fellows. A Magventure TMS therapy system will be used to deliver TMS treatments by the PI, TMS technician or Psychiatric Fellows under clinical supervision of Dr. McDonald.

5.2 N/A

6.0 Procedures Involved*

6.1 The primary intervention is a randomized, double-blind clinical trial for a 10-day treatment (2 per day with 30 minute break, 20 sessions in total) of active TMS or sham control. Initial screening for eligibility will occur in the primary care clinics of Grady Memorial Hospital through a parent project, the Grady Trauma Project (GTP, IRB00078593). After initial screening in the primary care clinics through the GTP to determine eligibility for the study associated with this study and appropriate informed consent procedures, subjects will participate in a pre-intervention assessment. This visit will start with confirmation of inclusion and exclusion criteria, pregnancy test in childbearing age women, and gathering of verbal and written informed consent. Following the pre-intervention assessment, participants will be randomly assigned using a random number generator to either the active TMS or sham control TMS.

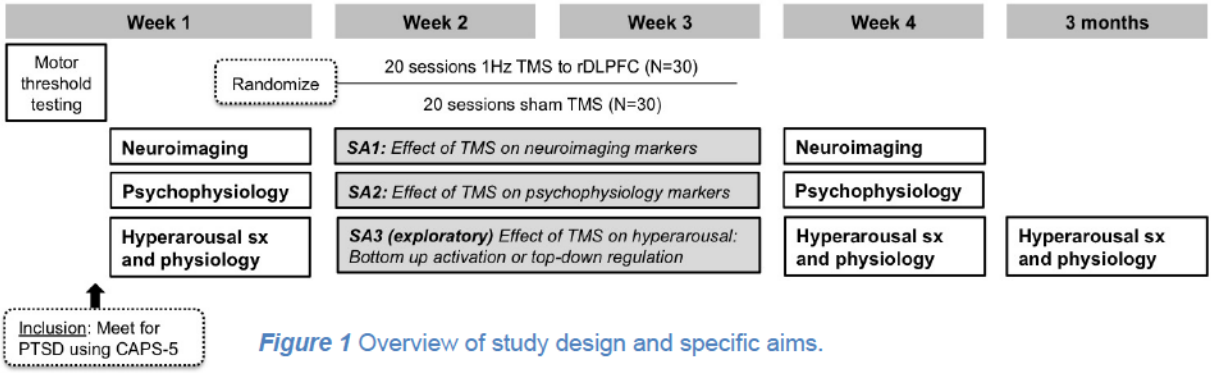


Figure 1 Overview of study design and specific aims.

6.2 Participants start with the pre-intervention assessments. The TMS motor threshold testing will be used to define the intensity for the TMS treatment. Participants also complete a neuroimaging, psychophysiological and clinical assessment in week 1 (before the TMS treatment) and again in week 4 (after the TMS treatment phase) as well as an optional EEG assessment. At 3 months, participants are invited for a long-term follow-up. As part of the parent project (GTP), PCL-5 and BDI will be collected before participants are enrolled in this study. In addition to the measures included in Table 1, subjective units of distress (SUDs) ratings will be assessed prior to and after each TMS or sham session as well as the optional EEG assessment. The days of the week presented in the example will be followed as closely as possible, but if participants are not able to do all TMS or sham sessions in two weeks, the remaining sessions (maximum of 3) can be completed in week 4.

6.3 **Emory Multimodal Learning Test (EMLT)** – At one visit before and one visit after the 10 TMS visits, the participant will watch a series of videos showing a normal life activity (e.g., eating a meal at a restaurant, a

volleyball match), during which a professional actor stops, introduces themselves to the viewer, and tells some kind of brief story. The subject is required to learn the face, name, location, story, and incidental detail as best they can. This attempts to capture how real-world memories are formed. This is tested over a delay of 30 minutes. Participants will be given the option to complete longer term follow-ups of recall only, which can be completed by the subject from their home. This is done with input from their Emory assessor, which can be provided over zoom. Eye tracking can be utilized with this measure and it can be given with a virtual reality headset.

Table 1 Schedule for a study participant.

	Week 1	**Week 2**	**Week 3**	**Week 4**	**3 months**
Monday	*TMS MT testing*	TMS or sham	TMS or sham, EEG	Psychophysiology CAPS-5, MINI	CAPS-5, PCL-5, BDI, CD-Risc, ISI, eSense
Tuesday		TMS or sham, EEG	TMS or sham	MRI scan, BDI, CD-Risc, ISI, PCL-5, eSense, EEG	
Wednesday		TMS or sham	TMS or sham, EEG		
Thursday	CAPS-5, MINI, PCL-5 - *no PTSD, discontinue* Psychophysiology	TMS or sham, EEG	TMS or sham		
Friday	MRI scan, BDI, CD-Risc, ISI, PCL-5, eSense, EEG	TMS or sham BDI, PCL-5	TMS or sham BDI, PCL-5, EEG		

Week 1: The first visit will start with the motor threshold (MT) testing. Participants will be told that "this is a treatment where we find the dose, some people may benefit from this, most won't". The reason is to see if participants show a strong sham response. All participants will be invited for a clinical interview (clinician-administered PTSD scale; CAPS, PCL-5) with a clinical psychologist later that week. If the participant does not meet DSM-5 criteria for PTSD based on this interview (for example as a consequence of the sham response), their participation in the study will be discontinued. If the score Psychophysiological assessments will be performed on the same day. Participants will be invited for the MRI scan on a separate day. No adverse events from the MRI will be expected, but adverse events will be assessed

Week 2+3: Patients will be scheduled for treatment sessions for the same time each day. Participants will be invited for 90-minute sessions on 10 consecutive weekdays, and each session will consist of two 30-minute treatment sessions with a 10-minute break in between. All patients will complete BDI and PCL-5 assessments at end of each week. At each visit, we will assess for any adverse events. No adverse events from the TMS treatment will be expected, but safety will be assessed at every treatment visit by recording spontaneous adverse event reports that will be coded using the current version of the *Medical Dictionary for Regulatory Activities.*

Week 4: PTSD symptoms using the CAPS-5 will be assessed. On the same day the psychophysiological assessment will be performed. The next day participants will be invited for a second MRI scan. On this day, PTSD symptoms will be assessed with the PCL-5 and skin conductance response (SCR) during trauma memory reactivation. Additionally, depression symptoms will be assessed using the BDI, resiliency using the CD-Risc and sleep disturbance using the ISI.
Month 3: PTSD symptoms using the PCL-5 and CAPS-5 and skin conductance response (SCR) during trauma memory reactivation will again be assessed. Depression symptoms will be assessed using the BDI, resiliency using the CD-Risc and sleep disturbance using the ISI. Adverse events will be assessed.

6.4 As a guard against risk of confidentiality, all information will be stored in locked files in a locked research area that can only be accessed by research personnel. No names or identifying information will be used in publications that result from this research. Except as may be required by law or for purposes of protecting the safety of the patient or others, identifying information will not be released to any outside party (beyond those immediately connected with the study) without written consent from the subject. In cases where data are stored on computers, no data containing identifiers or PHI will be stored on hard drives—only on removable media, which will be removed from the computer when not in use. All databases will be password protected.

TMS is an FDA-approved treatment for pharmaco-resistant depression and is widely used in clinical and research settings. To protect against risks related to TMS, we will follow established safety guidelines for the use of TMS in humans (82). We conduct a standard TMS safety screen (as part of inclusion criteria). We will ask participants before each session if they have used drugs or alcohol or medication in the last 24 hours to assess any incapacity for TMS. Furthermore, we will conduct a urine pregnancy test on all female of childbearing age during informed consent, and before motor threshold testing) and require that they are on reliable birth control. If they are not on reliable birth control, a pregnancy test will be conducted at the beginning of each TMS treatment week. Any participant with a positive urine pregnancy result would be discontinued from the study, and referred to Obstetrics and Gynecology through Grady Health System. Safety will be assessed at every treatment visit by recording spontaneous adverse event reports that will be coded using the current version of the Medical Dictionary for Regulatory Activities.

With regard to risk of distress associated with interviews, the participants will be told that they can stop the process at any point if they become overwhelmed or fatigued. Following their participation in the research, participants will be debriefed and have an opportunity to discuss their participation in the research and ask any questions they may have for the

interviewer. If they request it, a list of resources (local mental health services) will be provided to them after participation.

In the case of participants who present as suicidal or who are in crisis, a licensed clinical psychologist or psychiatrist who is part of the GTP will be contacted. This contact information is available to everyone working as part the GTP and there is always a clinician on site or on available by phone. The clinician will assess suicidality using the Columbia Suicide Severity Rating Scale and assessment of risk and protective factors. If participants exhibit active suicidality as assessed by the clinician, they will be referred for immediate admittance and assessment at the Grady Hospital Emergency Psychiatric Service.

With regard to risks associated with the MRI, participants will have ready access to the research team, should they experience any problems. Further, during scanning the participant can be seen at all times by the research coordinator standing in front of the bore or through the window between the control room and the scanner room. The participant can communicate with the control room personnel via an intercom at the operating console and will be handed a squeeze ball to set out an alarm for emergencies upon which the scanner will be stopped immediately. The participant can be removed immediately from the scanner if necessary or if they request removal. Participants will wear earplugs to minimize exposure to excessively loud noises, and the length of each MR study will not exceed 60 minutes. No adverse events from the MRI will be expected, but adverse events will be assessed. All MRI scans will be reviewed by multiple qualified MRI experts. The study MRI processing technician has over 15 years of experience looking at scans and will examine each image closely. The study PI will also examine each scan. Lastly co-investigator Stevens has over 10 years of experience with MRI scans and will review scans for safety as well. Emory research imaging facilities are overseen by qualified Radiologists who are also always on call for review of any images that raise question or concern for the study team.

The mobile device used to assess the skin conductance response (eSense) is approved for consumer use.

6.5 All measures that will be collected in this study have been widely used in this specific population.

Neuroimaging measures [Specific Aim 1]. Pre- and post-treatment neuroimaging data will be collected on a 3T Siemens Trio (Siemens, Malvern, PA), using a 32-channel head coil (**Table 2**). To enhance reproducibility, acquisition parameters will follow the Human Connectome Project (HCP). Although HCP has a specially developed scanner that is specific to that project (Siemens Connectom), we will follow the same philosophy for data acquisition, maximizing spatial and temporal

resolution. We will match the parameters used in the HCP S1200 release as closely as possible. Furthermore, in Year 2, I will attend the HCP summer training institute, which is conducted yearly, to train on the latest methods being implemented in the HCP community. Structural MRI: T1w MPRAGE and matching T2w SPACE sequences will be collected for the assessment of gray matter anatomy (TR=2400ms, TE=2.14ms, FA=7°, 0.8mm^3 voxel size). Parallel imaging (GRAPPA) with an acceleration factor of 2 will be used, for a total scan time of ~8 minutes. Structural Connectivitiy: Diffusion tensor imaging (64 slies, TR=13500ms, TEI=104ms, TE2=154.92ms, 2mm^3 voxel size) will be performed to understand structural integrity of white matter tracts connecting different brain regions. Functional MRI: The same acquisition parameters will be used for all fMRI tasks. T2* echo-planar images will be collected with 72 slices in a descending interleaved sequence (TR=1000ms, TE=33.10ms, 2mm^3 voxel size), and multiband acceleration factor of 8. Resting state (10 min): Participants are asked to look at a white cross on a black background for the duration of the task, lay still, let their mind wander and not fall asleep. Resting state scans will be used to measure FC during rest. Fear Conditioning (7 min) task: This paradigm is a modification of a well-validated paradigm (Jovanovic et al., 2012) to measure fear learning in one session. Participants are shown pictures of an office with a yellow or blue lamp, and are fear conditioned to an aversive sound paired either with a yellow or a blue lamp. In the extinction phase, participants see the same pictures of the office with either the blue and yellow lamp, and additionally see a different office with either the blue of yellow lamp. The primary outcome variable in this task will be amygdala, dACC, and response and FC for the contrast CS+ > CS- during both fear conditioning and extinction. Response inhibition task (10min): Subjects will be asked to respond to the Go trials (white X or O on black screen), but to withhold their response to the NoGo trials (red rectangle in the background). Only correct Go and NoGo trials will be included in the analyses, and the contrast NoGo > Go will be used. Fearful faces task (5 min): Participants will view 15 blocks of fearful face stimuli and 15 blocks of neutral face stimuli, with emotion condition randomly interleaved. Within each block, 8 face stimuli are presented, with the face presented for 500ms, followed by a 500ms inter-trial interval (ITI). After every 10th block, participants are instructed to rest and relax for 10s. The primary outcome variable in this task will be each individual's amygdala, vmPFC and dorsal ACC reactivity and connectivity for the Fearful Face > Neutral Face contrast.

Psychophysiological measures [Specific Aim 2]. A fear conditioning and extinction paradigm will be conducted in a startle booth. We will follow the protocol developed by Dr. Jovanovic (study collaborator), which has been used successfully in trauma populations for many years. Acoustic Startle Response (eye blink) will be measured via electromyography (EMG) of the

right orbicularis oculi muscle. Two 5mm Ag/AgCl pre-gelled disposable electrodes will be positioned approximately 1cm under the pupil and 1cm below the lateral canthus. All resistances will be less than 6 kilo-ohms. EMG activity will be acquired at a sampling rate of 1kHz, amplified and digitized using the EMG module of the Biopac MP150. The startle probe (noise burst) will be a 106-dB SPL, 40-ms burst of broadband noise with near instantaneous rise time. The aversive stimulus (US) will be a 250ms airblast with an intensity of 140 p.s.i. directed to the larynx. The conditioned stimuli (CS) will be different colored shapes appearing on a computer monitor in front of the participant, presented for 6 seconds. The startle probe will then be delivered and will be followed by the airblast 500ms later. One CS will be paired with the airblast (CS+) on 100% of the trials, while the other will not (CS-). The session will consist of 3 blocks, each with 4 CS+ trials, 4 CS- trials, and 4 noise alone (NA, no CS presented during startle probe) trials, for a total of 36 startle trials. Ten minutes after conditioning, the extinction session will present the same stimuli but the CS+ will no longer be paired with the airblast US. Extinction will consist of 4 blocks of 4 trials of each type for a total of 48 trials. In all phases of the experiment, inter-trial intervals will be randomized between 9 and 22 seconds. The subjects will respond on a response keypad (Cedrus, Inc.) on every CS trial to provide US expectancy data on a trial-by-trial basis. Skin conductance (SC) will be acquired during a 2 min baseline, and during the Standard Trauma Interview (STI) using the eSense SC system (Mindfield Biosystems, Inc., Berlin, Germany) on an iPad (iOS10) as previously validated in PTSD (Hinrichs et al., 2017). The eSense application will be launched on the study iPad and two Ag/AgCl finger electrodes will be attached to the middle phalanges of the middle and index finger with Velcro straps. Isotonic paste will be added to the electrodes prior to attaching to the fingers to ensure good contact with the skin. eSense acquires data at a sampling rate of 10 Hz and exports csv files for analyses.

EEG session. The EEG session will be presented to participants as an OPTIONAL sub-study. If the participant selects to participate the EEG session will occur in Emory Brain Health Center, concurrent with the TMS treatment sessions. There will be 6 total sessions of EEG recording which includes one pretreatment and one posttreatment as well as four sessions of EEG recording every other TMS session(i.e., four days of ten-days TMS treatment). In all 6 EEG recording sessions, EEG signals will be recorded before and after the study proceedure each day of EEG recording. Each EEG recording session would take 5 minutes. We will use the EMOTIV EPOC X 14 Channel Mobile Brainware (A commercially available device). This device provides 14 EEG channels, including AF3, F7, F3, FC5, T7, P7, O1, O2, P8, T8, FC6, F4, F8, AF4. The EEG setup will include first showing the device to the participant and explaining how it will feel ("it will feel tight and dry and if it pokes or feels uncomfortable, tell us so we can fix it"). Following

this, we will measure the participant's head for optimal device placement. A trained experimenter will gently place the device on the participant's head and adjust the fit and arrangement.

Psychological measures [Specific Aim 3, inclusion/exclusion criteria and covariate analyses] are mostly self-report measures (except CAPS and MINI), but will be collected by experiments who read the scales to prevent literacy bias.

Instrument	Measurement
MINI International Neuropsychiatric Interview for DSM-5 (MINI; Sheehan et al., 1998)	Axis-I diagnosis (except PTSD module)
Clinician Administered PTSD Scale (CAPS-5; Blake et al., 2015)	PTSD diagnosis according to DSM-5
PTSD Checklist, weekly version (PCL-5; Blevins et al., 2015)	Dimensional measures of PTSD symptoms
Beck Depression Inventory (BDI; Beck et al., 1961)	Dimensional measures of depression symptoms
Childhood Trauma Questionnaire (CTQ; Bernstein et al., 1997)	Self-report measure of childhood abuse and neglect
Traumatic Events Interview (TEI; Binder et al., 2008)	Inventory of exposure to criterion A trauma events
Alcohol Use Disorders Identification Test (AUDIT; Babor et al., 2001), Drug Abuse Screening Test (DAST-10; Yudko et al., 2007)	Substance use disorders
Subjective Units of Distress Scale (SUD; Rauch et al., 2018)	Within- and between-session patient-reported distress
Standard Trauma Interview (STI; Rothbaum et al., 1992)	Demographics, and description of trauma and severity
Insomnia Severity Index (ISI; Morin)	Brief self-report measure assessing sleep disturbance
Connor-Davidson Resilience Scale (CD-Risc; Connor-Davidson)	Brief Self-Report measure on psychological resiliency.

6.6 No long-term data past the scheduled 3-month visit will be collected.

6.7 N/A

7.0 Data and Specimen Banking* N/A ☐

8.0 Sharing of Results with Participants*

8.1 Results will not be shared with participants.

8.2 N/A

8.3 The MRI scan could reveal incidental findings such as potential abnormalities in the brain. The MRI scans are not assessed by healthcare professionals qualified to read the scans, and researchers are not qualified to read the scans and will not look for potential abnormalities. However, the participant will be informed of an incidental finding as observed by the research team and asked if they want the scan to be sent to a qualified health professional for further assessment and potential treatment.

8.4 All MRI scans will be reviewed by multiple qualified MRI experts. The study MRI processing technician has over 15 years of experience looking at scans and will examine each image closely. The study PI will also examine each scan. Lastly co-investigator Stevens has over 10 years of experience with MRI scans and will review scans for safety as well. Emory research imaging facilities are overseen by qualified Radiologists who are also always on call for review of any images that raise question or concern for the study team. If an MRI scan reveals a potential abnormality as observed by the MRI operator, PI or a study member, the MRI operator and the PI both look at the scan, and contact the director of the imaging center if they agree it looks abnormal. If all decide the MRI looks abnormal and a health professional should look at the scan, the patient will be contacted and will be asked if they want their scan to be sent to a qualified health professional for further assessment. The following information is included in the informed consent: "You will undergo an MRI scan for research purposes only. The research does not require health professionals to read the scan. The researchers are not qualified to interpret the images for healthcare purposes. Do not rely on the scan for clinical or diagnostic purposes. However, if the researchers have a question about something they see on the scan they will tell you, and ask you if you want the scan to be assessed by a qualified health professional for review and be referred for potential further medical treatment. You or your insurance company may have to pay for the review and any such treatment.".

9.0 Study Timelines*

Each participant will take 4 weeks to complete the majority of the study protocol, and at 3 months there is one follow-up visit.

As shown in the table below, with the first enrollment at 6 months, and a goal of enrolling ~2 participants per month, we will have 13 participants enrolled and we expect 10 of them to complete the study accounting for 25% dropout. Because of the longitudinal design and 3-month follow-up, 5 participants are expected to have completed the study at the end of year 1. Participant recruitment will be completed by month 6 of Year 4, with follow-up visits continuing into month 9. To complete the study by the end of year 5, we will adhere to the following timeline:

Table 1 Study timeline

	Year 1	Year 2	Year 3	Year 4	Year 5
Study goals	IRB approval		Preliminary analyses	Analyze data	Analyze data Publish results
Subjects per Year *Enrolled* *Expected to complete* *Completed*	 N=13 N=10 N=5	 N=27 N=20 N=15	 N=27 N=20 N=15	 N=13 N=10 N=10	
Subjects in Total *Enrolled* *Expected to complete* *Completed*	 N=13 N=10 N=5	 N=40 N=30 N=25	 N=67 N=50 N=45	 N=80 N=60 **N=60**	

10.0 Inclusion and Exclusion Criteria*

10.1 Participants will be recruited from a larger study, the Grady Trauma Project (GTP – IRB00078593). The eligibility for the current study will be assessed as part of the larger GTP, and anyone who meets study-specific eligibility criteria and who has consented to be contacted for future research will be scheduled to come in an initial visit for additional Inclusion/Exclusion assessment and study consent.

10.2 ***Inclusion criteria:***

- Men and women 18-65 years of age.
- **Meet for partial PTSD, defined as 3 out of 4 symptom clusters always including cluster E (alterations in arousal and reactivity) according to the DSM-5 criteria using the Clinician-Administered PTSD Scale (CAPS-5).**
- Capable and willing to provide informed consent.
- Able to adhere to the treatment schedule.

Exclusion criteria*:*

- Having active suicidal intent or plan as defined by a positive answer to questions 4 and/or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS): Screening version; or in the clinician's opinion, is likely to attempt suicide within the next six months.Unstable psychotropic medication status. Participants taking psychotropic medications (i.e.,antidepressants, antipsychotics, benzodiazepines and anticonvulsants, etc.) can be enrolled in the study as long as medication type and dose has been stable for at least 6 weeks, and additionally, medication type or dose does not change during the course of the study.
- Lifetime diagnosis of psychotic disorder or bipolar I disorder per diagnostic interview. .

- Diagnosed with the following conditions: a neurological disorder, including a history of seizures, cerebrovascular disease, primary or secondary tumors in CNS, stroke, cerebral aneurysm or movement disorder or any lifetime history of loss of consciousness for more than 5 minutes due to head injury.
- History of cranial surgery, metallic particles in the eye or head (exclusive of mouth), implanted cardiac pacemaker or any intra-cardiac lines, implanted neurostimulators, intra-cranial implants (e.g., aneurysm clips, shunts, stimulators, cochlear implants, or electrodes) or implanted medical pumps.
- Current substance abuse or dependence as indicated by a score of 6 or higher on the Drug Abuse Screening Test (DAST).
- Current alcohol abuse or dependence as indicated by a score of 8 or higher on the Alcohol Use Disorder Identification Test (AUDIT).
- Being pregnant or a positive pregnancy test at the beginning of each TMS treatment week for sexually active women of childbearing age who are on reliable birth control.
- Currently participating in another clinical study or enrolled in another clinical study within 30 days prior to this study or started (new) treatment for PTSD within 3 months prior to this study.
- Previously treated with TMS.

10.3 The study will not include adults unable to consent, individuals who are not yet adults (infants, children, teenagers), pregnant women or prisoners.

10.4 We will register and maintain records on the proposed study with ClinicalTrials.gov and adhere with all proper dissemination guidelines set forth by the NIH. The PI will establish a training protocol for how to conduct TMS for PTSD based on the results of this study, which can be disseminated to others with TMS experience. The PI will also supervise the writing of peer-reviewed manuscripts from the proposed study that will acknowledge the proposed funding and registration with clinicaltrials.gov. We will appropriately disseminate our findings with colleagues at scholarly conferences over the period of the study. Informed consent documents for the clinical trial will include a specific statement relating to posting of clinical trial information at ClinicalTrails.gov, and Emory University has an internal policy in place to ensure that clinical trials registration and results reporting occur in compliance with policy requirements.

11.0 Vulnerable Populations* N/A ☐

12.0 Local Number of Participants

12.1 We anticipate having a final sample of 60 patients with PTSD at time of enrollment as defined by the DSM-5 criteria.

12.2 Based on historic data from GTP, we anticipate 10 screens/week for 3 years, N=1560 screens, estimated 46% will have PTSD (Gillespie et al., 2009), 10-15% will be eligible and interested, N=80 will be enrolled and randomized, 25% estimated dropout, N=60 completers. We will exclude for psychotropic medication use, but recruitment will not be impacted as the numbers for medication use are typically low in this population (3.7%, N=181 in sample of N=4931). Dropout is expected to be comparable to other longitudinal studies (15-25%) and the prior intervention studies (23-25%) taken into account that this study has more visits, but in a shorter time period. Therefore, N=80 patients will be enrolled in the study.

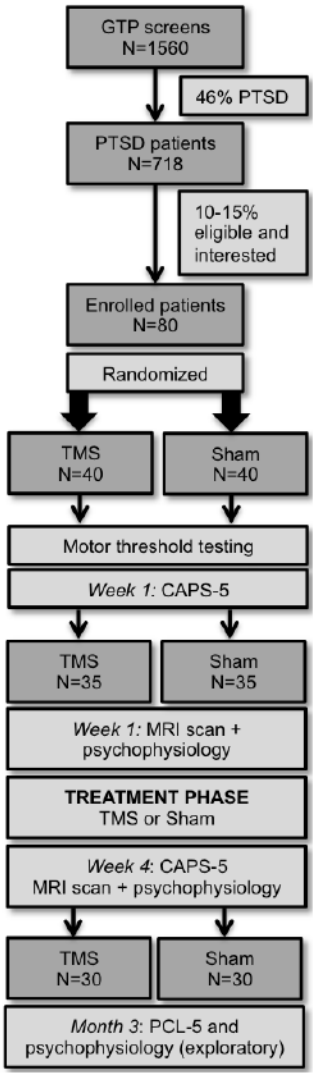


Figure 1 Flowchart of progression through study.

13.0 Recruitment Methods

13.1 Participants will be recruited through the Grady Trauma Project (GTP). Since 2005, GTP has enrolled over 12,000 participants from a pool of patients receiving care at the general medical clinics at the Grady Memorial Hospital, a publicly funded, urban care center serving a predominantly low-income inner-city African American population. Based on our previous work at this institution, we anticipate that participants will have a high rate of exposure to diverse types of trauma, which will allow for assessment of the effects of trauma across a range of severity levels and types. Individuals of all races and ethnic backgrounds are eligible for the study. However, the patient population is primarily composed of low SES (87% with monthly household income < $1000), minority individuals (>80% African American and 5-10% Hispanic.

13.2 Participants will be recruited from the GTP.

13.3 The PTSD checklist for DSM-5 (PCL-5) is collected as part of the GTP protocol. Scores on the PCL-5 will be used to identify PTSD patients who are enrolled in GTP. A checklist with other in- and exclusion criteria will be used to determine eligibility.

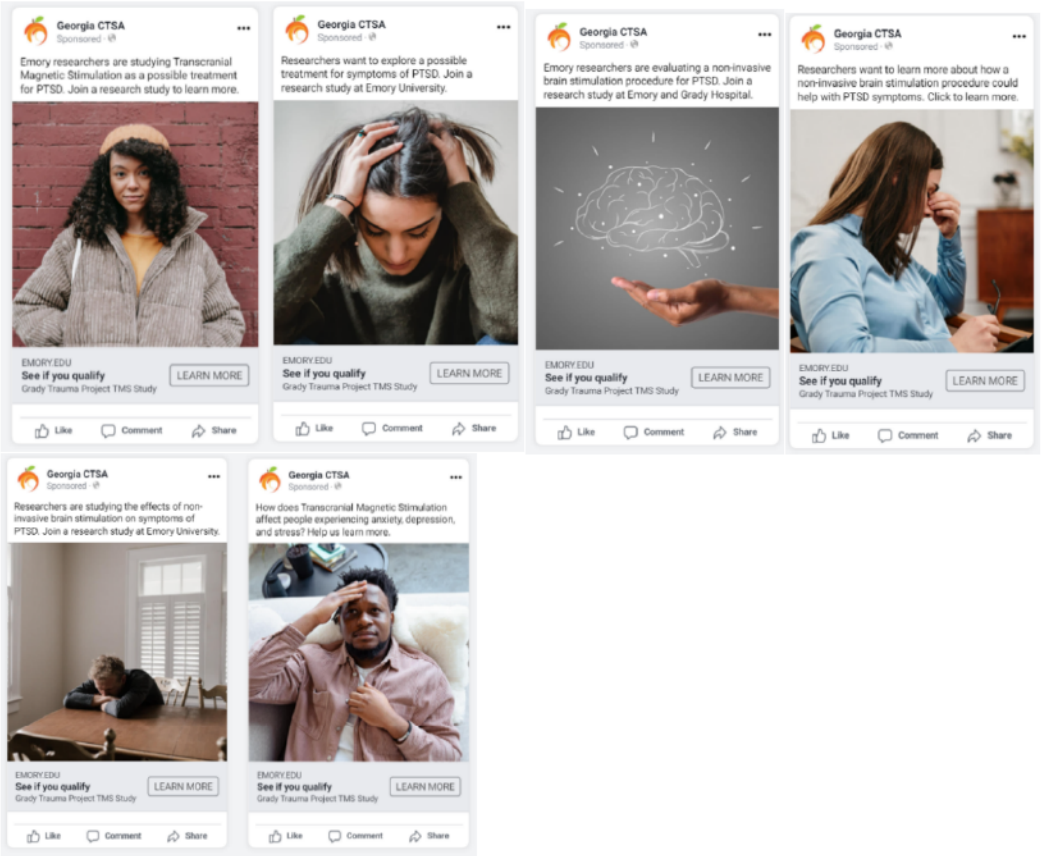
13.4 Fliers posted in the community and social media advertisements will be used for recruitment. Participants will also be recruited through the GTP from participants who indicate they are interested in future research.

Social Media Management Plan
PI: Sanne van Rooij
IRB Number: 00150226
Date submitted to IRB: 02/10/2022

1. The following social media sites will be used for recruitment:
    - Facebook
    - Instagram

The Georgia CTSA Recruitment Center will be responsible for posting and managing these social media ads.

2. Examples of advertisements that will be used:



3. The social media ads will link to Redcap landing page that asks for contact information and a survey to see if they will qualify for the study.

Screen shot of landing page:

4. Targeting criteria:
Location: United States: Atlanta (+25 mi) Georgia

Age: 18 – 64

People Who Match: Interests: Insomnia, Streaming media, Late-night talk show, African-American culture, Netflix or People (magazine), Relationship Status: Divorced or Widowed

13.5 We will compensate participants for time and travel. We will compensate participants $20 for the motor threshold testing, $30 for the each of the two clinical interviews and self-report measures collected (week 1, week 4), $30 for the each of the two psychophysiological assessment, $60 for each of the two MRI study visit, and $20 for each TMS visit (10 visits total) and $30 for the long-term follow-up visit including self-report measures and the short eSense psychophysiological assessment. Total participant payment is $490. Furthermore, participants will be offered transportation to Emory's Brain Health Center where motor threshold (MT) testing will be conducted

and TMS treatment will be delivered. $40 per treatment session per participant is budgeted. This money will not be paid to the participants, but used to pay uber rides.

		Payment	# of visits
Participant payments	MT testing	20	1
	TMS/therapy	20	10
	Interview, pre	30	1
	Interview, post	30	1
	Startle, pre	30	1
	Startle, post	30	1
	Scan, pre	60	1
	Scan, post	60	1
	EEG, each day	5	7
	FU assessment	30	1
	Total p.p		$525

We balanced 3 primary concerns in making our decisions about how much and when to pay participants: 1) the primary demand on participants in this study is number of visit and we want to compensate participants adequately for this time and provide transportation; 2) we do not want the amount of money to be coercive; and 3) we want to include participation from subjects across a full range of socioeconomic status. We thus chose an amount that we felt would be adequate to encourage the participation of patient across SES groups (e.g., not to have the sample skewed towards subjects willing to participate for an honorarium that would only be attractive to patients who are indigent, given that the study requires both a time commitment and willingness to talk about personal matters with a research interviewer.

14.0 Withdrawal of Participants*

14.1 N/A

14.2 Participation will be discontinued if the participant (1) does not meet DSM-5 criteria PTSD during the clinical interview in week 1 and (2) no shows for three visits in a row during the first weekParticipants will be thanked for their participation and paid for the parts of the study they have participated in.

Rationale: (1+3) After enrollment, the first day of the study included motor threshold (MT) testing, followed by a clinical interview a few days later. Participants who are extremely susceptible to sham may demonstrate a dramatic decrease in PTSD symptoms after the motor threshold testing, and may not meet criteria for PTSD during the clinical interview. Therefore, they will be discontinued from the study after the clinical interview to decrease the overall sham response rates. (2) Participants who do not show for 3 consecutive visits during the first week (MT testing, clinical interview, psychophysiological assessment or MRI scan) will be discontinued from the study. This will result in lower dropout rates once

the treatment is started as we have observed that individuals who reliably show up for several appointments in a short period of time are more likely to show for all appointments. Finally, the scan is the most expensive single component of the study and by discontinuing participants for the reasons described above before they have been scanned limits costs related to scans of patients who drop out of the study.

14.3 Participants can discontinue their participation at any given time during the study and will be reminded of this throughout the study. If a participant decides the discontinue from the research, they are asked if they agree to keep the collected data in the database. If not, then all their data will be removed. If they are willing to continue participation only in certain parts of the study, the PI decides if it is valuable to collect the data of the components of the study they are willing to participate in. In either scenario, a follow-up phone call will be made ~1 month after discontinuation to ensure safety of the participant and assess if the study has not negatively affected them. Participants are made aware that they will receive this phone call.

15.0 Risks to Participants*

15.1 One potential risk is that the participant may be asked to talk about prior experiences and events that may be emotionally difficult to discuss and may bring up distressing feelings. In addition to monitoring participants within the sessions, researchers will provide information at the first session of treatment for what the participant should do if they experience a significant increase in symptoms or have any emotional problems outside of their study visit. This information will include the PI's and study coordinator's work phone number where they can be reached during business hours (8:00am - 5:00pm), as well as the phone number for the Georgia Crisis and Access Line, which is a 24-hour hotline with licensed psychologists and social workers who can take crisis calls and provide immediate assistance should the participant need it. Throughout the study, participants will be reminded of these resources.

Risks related to transcranial magnetic stimulation treatment are minimal. TMS is used a lot and the risk profile is clear. Generalized seizures have been reported with the use of TMS, however, a recent study showed that this risk is very minimal and was reported as <0.02 seizures per 1000 sessions (4 seizures in 242,067 sessions) (Lerner et al., 2019). Moreover, the incidence of seizures for low-frequency TMS (1Hz or below, as proposed here) was 0. Importantly, these numbers reflect sessions conducted without elevated protocol or subject risk, and therefore individuals at known increased risk are not eligible for the study (see eligibility criteria).

There is minimal risk associated with MRI scans.

Risk of obtaining clinical information by interview, ratings, cognitive testing, and chart review. The only risk here involves potential loss of confidentiality.

Risks for the EEG are that participants may feel slightly uncomfortable due to the slight tightness of the device. All questions will be answered, and procedures explained to help alleviate any concerns or anxieties.

15.2 TMS is used a lot and the risk profile is clear, therefore there are no unforeseen risks.

15.3 Pregnant women are not included in the study. All female participants of childbearing age will conduct a pregnancy test at time of informed consent. Additionally, female participants who are sexually active need to be on reliable birth control, otherwise, pregnancy tests will be conducted at the beginning of each TMS treatment week.

15.4 N/A

16.0 Potential Benefits to Participants*

16.1 N/A

16.2 The study is not designed to benefit the individual participants.

17.0 Data Management* and Confidentiality

17.1 **Specific Aim 1: Examine the effect of TMS on PTSD neuroimaging biomarkers. Hypothesis 1a**: TMS vs. sham will increase inhibition-related ventromedial (vm)PFC and hippocampal activation and decrease amygdala activation during fear conditioning and inhibition at post- as compared to pretreatment. Specifically, TMS vs. sham will (I) decrease amygdala and dACC activity during a) fear acquisition (CS+ > CS-) and b) fearful faces > neutral faces, (II) increase hippocampal and vmPFC activation during a) fear inhibition (CS+ > CS-) and b) response inhibition (NoGo > Go). First level contrasts for each task as described above will also be created using SPM12. For second level analyses, both region of interest (ROI) and secondary whole brain analyses will be conducted. First, ROI analyses will be conducted by extracting the contrast estimates for the amygdala, vmPFC, dACC and hippocampus. Repeated measures General Linear Model (GLM) will be conducted with pre- vs. post-treatment as within subjects factor, TMS vs. sham as independent between group variable, pre-treatment PTSD as covariate, and the ROIs for each contrast as dependent variables. Second, rigorous clustering and voxel-based thresholding parameters (FWE-corrected) will be used to examine whole brain patterns of activation using the same repeated measures design. **Hypothesis 1b**: TMS vs. sham will increase vmPFC-amygdala and DLPFC-amygdala functional connectivity (FC). This hypothesis will be tested in two ways: (I) Psychophysiological interaction analyses (Friston et al., 1997; Gitelman et

al., 2003) will be used to examine the change in connectivity measures from pre- to post-treatment for task-based FC using the amygdala as a seed and the vmPFC and DLPFC as ROIs. (II) Seed-based resting state FC analyses (Whitfield-Gabrieli & Nieto-Castanon, 2012) will be conducted using the amygdala as a seed. For both analyses, a repeated measures group by time GLM controlling for baseline PTSD symptoms will be used. Furthermore, TMS vs. sham is expected to increase the brain's dynamic FC reflected by more state transitions. To test this hypothesis, (III) data-driven approach using independent component analyses (ICA) will be used to assess the effects of TMS vs. sham on whole brain FC during resting state (analyzed using the GIFT software developed by Dr. Calhoun's group (Calhoun et al., 2001; Rachakonda et al., 2010). Furthermore, static and dynamic connectivity analyses (Allen et al., 2012; Hutchison et al., 2013) will be conducted to assess the effect of TMS on the brain's modularity versus flexibility. **Hypothesis 1c**: Subjects whose DLPFC TMS target, as defined with structural neuronavigation, was (more) functionally connected with the amygdala will show more effect of TMS on H1a and H1b. To test this hypothesis, the exact targeted location (MNI coordinates 40, 28, 44) will be used as a seed in FC analyses to assess connectivity with the amygdala. Within the subjects who received active TMS, this FC measure will be related to the effect of TMS on the biomarkers described in H1a and H1b by including it as a predictor in the repeated measures GLMs.

Specific Aim 2: Examine the effect of TMS on PTSD psychophysiology biomarkers. Hypothesis 2a: TMS vs. sham will reduce fear-potentiated startle (FPS) responses to safety cues from pre to posttreatment. Specifically, over treatment TMS vs. sham will (1) reduce general FPS response to both safety and danger cues, and (2) increase discrimination, reflected by a smaller FPS response to safety than to danger cues. MindWare software will be used to analyze recorded autonomic data during the fear extinction task. The primary outcome of interest will be average startle reflex electromyography magnitude (eye blink; in microvolts). A 2 x 2 x 2 repeated measures GLM will be used with pre- vs. post-treatment, and safety vs. danger cues as two within subjects factors, and TMS vs. sham as independent between group variable, pre-treatment PTSD as covariate and FPS magnitude as dependent variable. **Hypothesis 2b**: TMS vs. sham will reduce SCR to trauma cues pre compared to post-treatment. TMS will reduce the SCR during trauma recollection over treatment resulting in a smaller difference score between trauma recollection and baseline. For the eSense SCR analyses the difference score of the peak during trauma recollection and the peak during baseline will be calculated. A repeated measures group by time GLM controlling for baseline PTSD symptoms will be applied. **Hypothesis 2c**: Similar to H1c, those subjects with increased FC between the DLPFC TMS target and

amygdala will show more effect of TMS on H2a and H2b. The same FC measure as calculated in H1c will be included in the repeated measures GLMs in the subjects who received active TMS to assess the effect of FC on psychophysiology biomarkers.

Exploratory Specific Aim 3: Assess the effect of TMS on PTSD hyperarousal symptoms and physiology SA1 and SA2 will be combined with clinical data and two competing hypotheses will be tested: **Hypothesis 3a:** Direct TMS effect: DLPFC stimulation directly reduces amygdala hyperactivation, which is reflected by reduced hyperarousal symptoms and physiology immediately post-treatment (week 4) compared to pretreatment in the TMS vs. the sham group. A repeated measures group by time (baseline and 4 weeks) GLM controlling for baseline PTSD symptoms will be applied using hyperarousal symptom cluster of the PCL-5 and the SCR to trauma cues in week 4 as outcome measures. Second, correlation analyses between change (pre to post) in PCL-5 and change in SCR and FPS to safety cues will be conducted. **Hypothesis 3b:** Indirect TMS effect: DLPFC stimulation improves PFC-amygdala FC, and a reduction in hyperarousal symptoms and physiology results from improved top-down regulation and is not observed until 3 months after treatment. It is hypothesized that TMS and control groups do not differ from pretreatment in hyperarousal symptoms and physiology at 4 weeks, but groups differ at 3 months, and a larger change in symptoms and physiology is related to improved prefrontal-amygdala FC. Again, a repeated measures group by time (baseline and 3 months) GLM controlling for baseline PTSD symptoms will be applied using hyperarousal symptom cluster of the PCL-5 and the SCR to trauma cues in month 3 as outcome measures. Second, correlation analyses between pre- to post-treatment change in amygdala-vmPFC and amygdala-DLPFC FC and change in SCR to trauma reminders and FPS to safety cues will be conducted.

17.2 The PI and research coordinator will do quality control checks on the data after the first 3 participants and then again after each 5 to ensure that all forms are being complete accurately, there are no quality control issues that need to be addressed, etc.

17.3 Describe how data or specimens will be handled study-wide:

- All data will be stored in either REDCap (self-report and clinical data) or on the Emory trusted server (Physiology and MRI data)
- Data will be stored in closed systems with access only for study team members on REDCap or the Emory trusted server
- Identifiable data will only be stored for the length of the study (anticipated to be 5 years) plus any unanticipated delay time. If data is retained after this time it will be de-identified.
- Study team members will have access to the data.

- The PI is ultimately responsible for the receipt of the data and storage to the appropriate locations.
- Data will not be transported as it will be stored to the appropriate online storage from its collection point.

18.0 Provisions to Monitor the Data to Ensure the Safety of Participants*

This section is required when research involves more than Minimal Risk to participants.

- This study will employ a Data Safety Monitoring Board and a comprehensive adverse events (AEs) reporting plan to minimize risks to the subjects. **Data Safety Monitoring Board (DSMB)**: The DSMB will act in an advisory capacity to the National Institutes of Health (NIH) to monitor participant safety in this Phase 2 clinical trial involving administration of transcranial magnetic stimulation (TMS) for the purposes of understanding its effects on brain function in patients with PTSD. The DSMB will be composed of:
- **Noah Philip, M.D.** (chair), Associate Professor, Associate Professor of Psychiatry and Human Behavior at the Alpert Medical School of Brown University
- **Andrew Kozel, M.D., M.S.C.R.** (member), Professor, Department of Behavioral Sciences and Social Medicine, Florida State University College of Medicine
- **Lauren Sippel, Ph.D.** (member), Assistant Professor, Department of Psychiatry, Geisel School of Medicine at Dartmouth
- **Christine Rabinak, Ph.D.** (member), Associate Professor, College of Pharmacy and Health Sciences, Wayne State University

18.1 . The DSMB will receive blinded and unblinded reports on study progress prepared by the PI, and will review safety data annually. Reports will include adverse events and protocol deviations.

In addition to the DSMB, Mentor William McDonald, M.D. (Professor of Psychiatry) will be responsible for the daily progress and safety of each participant while they are enrolled in the proposed study. The primary experimental component of this study will occur at the Emory Brain Health Center Clinical Research Site of the Georgia Clinical and Translational Science Alliance (GCTSA), where Dr. McDonald is located and treatment will be delivered by the PI under close supervision of Dr. McDonald. The TMS procedure is standardized and is used on a weekly basis as an FDA-approved treatment for Major Depressive Disorder. In case of an emergency, any immediate safety concern can be addressed by the Dr. McDonald or trained Brain Healthcare staff. Other procedures associated with this study, i.e., pre- and post-treatments neuroimaging, psychophysiological and clinical assessments will take place at Emory University's main campus and Grady campus, where any immediate safety concern can be addressed by Grady Hospital and Emory Healthcare staff.

Data will be reviewed regularly by internal audit. The study coordinator and PI will review records monthly on both REDCap as well as any paper forms for completeness and legibility as well as to collate any safety concerns for prompt reporting to the DSMB and Dr. McDonald.

Any adverse event will be carefully documented, followed, and submitted to the Emory IRB via the "Reportable Event Form." All data collection and monitoring will be in compliance with the Emory University Clinical Trials Guidebook. To adhere to HIPAA guidelines about confidentiality in collecting and disseminating human data, all data for a patient is de-identified before any researcher obtains it for analysis. Any publication or presentation that uses the data from participants in this study will use fully de-identified data. All members of this study have completed the Collaborative IRB Training Initiative (CITI) tutorial on the responsible conduct of human research, as well as the good clinical practice module repeated every 3 years.

The proposed study will be registered with Clinicaltrials.gov prior to enrolling the first participant, and results will be reported through the Clinicaltrials.gov infrastructure as prescribed. The execution of this study involves persons from Emory University (EU), and only EU members recruit potential participants (Grady Memorial Hospital patients) and collect any de-identified or personally identifiable data before it is de-identified for other researchers. Since the main research, such as recruitment and data collection, for this study occurs at EU and since the only review and approval of this protocol is by the Emory Institutional Review Board (IRB), all EU members, especially the PI (SVR) accepts full responsibility for data collected by the proposed study. The members of the mentor team participate in the analysis of only de-identified data in collaboration with Dr. van Rooij.

Adverse Events Definitions: The participants enrolled in this study are PTSD patients (18-65 years) recruited from a population at heightened risk for trauma and posttraumatic stress disorder. No adverse events related to TMS, MRI data collection, psychophysiological or clinical assessments are expected. However, we will closely monitor the participants and record unexpected and expected AEs and SAEs, as defined according to the Health and Human Services Office for Research Protections (https://www.hhs.gov/ohrp/regulations-and- policy/guidance/reviewing-unanticipated-problems/index.html#AA), as well as noting any clinical events as narrative data. If any Serious Adverse Event (SAE) occurs, a SAE form will be filled and submitted to the PI. The PI will report these events to the Independent Safety Monitor and the NIH, as well as Emory University's IRB and the Grady Hospital Research Council. These reports will be made within 5 business days of the event. All other serious, unexpected or unanticipated problems that are potentially related to the study will be

reported to the IRB, per local reporting guidelines. Operationally, this means that: 1) in the opinion of the PI, was there a causal relationship between the intervention and the serious event (i.e., there is a reasonable possibility that the event may have been caused by the TMS or participation in MRI or other aspects of the study); and 2) the serious event was unexpected (i.e., not identified in nature, severity or frequency in the current IRB approval research protocol or informed consent document). The PI will code events as: definitely related, possibly related, unsure, probably not related and definitely not related. Ongoing SAEs and AEs must be followed until resolved. A 30-day post-study follow up SAE/AE form will be included in subject monitoring. Unanticipated problems involving risks to participants or others will also be reported to the NIH Program Officer within 10 days of the event, and any AEs/SAEs determined unrelated to the study and any protocol violations will be summarized in the annual progress report to the NIH.

Expected Adverse Events: There are no expected AEs that are likely to be due to the study procedures.

Adverse Event Reporting: The adverse event data will be compiled by the PI and reported to the DSMB.

19.0 Provisions to Protect the Privacy Interests of Participants

19.1 Confidentiality will be protected throughout the study and following completion of the study. This will be done in a number of ways. First, all participants will be assigned a subject ID and all data gathered and session notes will only contain de-identified information and their subject ID. Also, participants will be informed of the confidential nature of the study and informed of the limitations of confidentiality. As a guard against risk of confidentiality, all information will be stored in locked files in a locked research area that can only be accessed by research personnel. No names or identifying information will be used in publications that result from this research. The only linkage between identifiable information about participants and their subject IDs will be kept on the informed consent forms, which will be separated from all other data and study materials and kept in a locked drawer in a locked office. Except as may be required by law or for purposes of protecting the safety of the patient or others, identifying information will not be released to any outside party (beyond those immediately connected with the study) without written consent from the subject. In cases where data are stored on computers, no data containing identifiers or PHI will be stored on hard drives—only on removable media, which will be removed from the computer when not in use. All databases will be password protected.

19.2 Study procedures will be explained to the participant during informed consent, and additionally at the beginning of each study day. Participants

will regularly be asked if they have any questions and will be reminded that that they can opt out of the study at any time.

19.3 All participant data will be stored on Redcap, and only study team members will have access to this data.

20.0 Economic Burden to Participants

20.1 There are no anticipated costs to the participants.

21.0 Consent Process

21.1 To obtain informed consent for the study, participants will receive a written description of the study, including risks, benefits, privacy, etc. In addition, a study co-investigator or research fellow will verbally describe the contents of the document and answer any questions. If the participant agrees to be in the study, he or she will indicate consent by signing the consent form on paper or in REDCap. Only participants who can give full authorized self-consent will be included in the study. We will not enroll any individual for whom consent needs to be obtained by a legally authorized individual. Consent will be obtained in a private office room with both the participant and a study co-investigator or research fellow present. A thorough discussion of the consent document along with questions about what the study will entail to ensure understanding of the participant will be conducted (average 15-20 minutes). Consent will be obtained prior to the motor threshold visit, on average a week, but at least 24 hours prior to the first session of TMS. Consent for videotaping will be separately reviewed with the study participant following consent to participate in the study and explanation that consent to videotape is voluntary and not necessary to participate in the study will be provided. Consent will be obtained by co-investigators or research fellows that have been fully trained in obtaining informed consent. Participants will be reminded before each visit that their consent is voluntary and can be removed at any time.

Non-English-Speaking Participants N/A ☐

Waiver or Alteration of Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception)

Participants who are not yet adults (infants, children, teenagers) N/A ☐

Cognitively Impaired Adults N/A ☐

Adults Unable to Consent N/A ☐

22.0 Process to Document Consent in Writing

22.1 Consent will be obtained from a written step-by-step consent form. To confirm the content of the consent discussion, an attestation form will be

signed by the consenting staff member and kept on file with the consent form.

22.2 N/A

22.3 N/A

23.0 Setting

23.1 Participants will be recruited from the Grady Trauma Project (GTP). The GTP is located in the basement level of the Glenn Building, an Emory building on the Grady Hospital Campus. There is a waiting area with coffee/tea/water facilities and bathrooms. There are five interview rooms that will be used for the clinical interviews. These rooms are private. Additionally, the Grady Neurophysiology Laboratory needed for the psychophysiological assessements is located in the GTP research area. This translational neuroscience laboratory is equipped with a psychophysiological suite that allows us to objectively assess psychophysiological biomarkers using state-of-the-art technology. The Neurophysiology laboratory occupies approximately 450 sq. feet divided into a subject prepping area and a testing room. The testing room has two large, 24 sq. feet sound-attenuating audiology booths for psychophysiological testing, with an adjacent control room for lab staff.

The TMS machine is located in the Emory Brain Health Center 9BHC). The TMS suite is located on the ground floor of the BHC and can be easily accessed from the parking lot. The suite has a waiting room, locked closet for file storage and two large treatment rooms (132 sqft each). One treatment room is dedicated to research and the other room for clinical treatments. TMS is used clinically for treatment-resistant depression (about 6 patients a day) and there is an ongoing research study being with the Emory Veteran's Program (Barbara Rothbaum, PI). There is research space available in the research suite for conducting this study.

MRI scanning for the proposed plan of research will take place in the 3,000 square foot Facility for Education and Research in Neuroscience (FERN) the centerpiece of which is a 3T Siemens Trio whole-body MRI scanner installed in 2013 in the Emory Psychology and Interdisciplinary Sciences building. This behavioral testing space; and computer room for data processing and analysis. FERN also features a waiting area and bathroom and locker facilities.

24.0 Resources Available

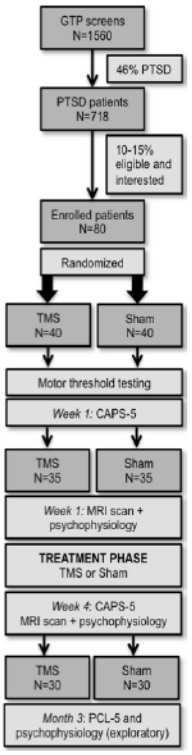


Figure 1 Flowchart of progression

- Based on historic data from GTP, we anticipate 10 screens/week for 3 years, N=1560 screens, estimated 46% will have PTSD (Gillespie et al., 2009), 10-15% will be eligible and interested, N=80 will be enrolled and randomized, 25% estimated dropout, N=60 completers. We will exclude for psychotropic medication use, but recruitment will not be impacted as the numbers for medication use are typically low in this population (3.7%, N=181 in sample of N=4931). Dropout is expected to be comparable to other longitudinal studies (15-25%) and the prior intervention studies (23-25%) taken into account that this study has more visits, but in a shorter time period. Therefore, N=80 patients will be enrolled in the study.
- The PI is funded for 75% of her total effort to conduct the study. In addition, there are funds for 50% of a Research Specialist.
- The facilities and other resources available for this research include everything needed to undertake and complete the proposed project successfully. **Grady Trauma Project (GTP):** This ongoing research study aims to investigate the effects of stress and trauma exposure and the relative contribution of genetic, neurobiological and environmental factors in a highly traumatized population recruited from Grady Memorial Hospital in Atlanta, GA. This project was initiated in 2005 with funding from NIH and Howard Hughes Medical Institute (HHMI) with Kerry Ressler, MD, PhD (mentor) as the principal investigator. The GTP team is composed of many psychiatrists, clinical psychologists, neuroscientists, trainees, and volunteers who examine non-psychiatric patients from the General Medical Clinic at Grady Memorial Hospital in Atlanta. The current data suggests that over 80% of this population has suffered significant trauma and approximately 46% have PTSD (Gillespie et al., 2009). The GTP has collected data from over 10,000 participants and is the largest civilian trauma/PTSD study in the world. It has also collected psychological assessments/structured diagnostic interviews from over 800 participants, and neuroimaging data from over 200 participants as part of this project. <u>GTP laboratory:</u> The PI will have access to all laboratory resources at the GTP site; the site includes a

full suite of offices and research rooms that cover a full floor of the Glenn Memorial Building, an Emory University on the Grady campus. The GTP offices are located across the street from Grady Memory Hospital, where my career mentor, Dr. Kaslow, is located. Furthermore, the PI will have assistance from the six full time staff members, a large group (over 10 students) of interns, and pre- and postdoctoral clinical psychologists. Clinical interviews will be conducted by pre- and post-doctoral clinical psychologists who will be closely supervised by Abigail Powers, PhD, Licensed Clinical Psychologist and Assistant Professor in the Department of Psychiatry and Behavioral Sciences at Emory University and Clinical Director of GTP. Office space: The PI has her office space within the GTP site, which includes a desk, computer, and printer. She will have full computer access and all computers are equipped with the latest software programs for data analysis, word processing, statistical analysis, and presentations. As the office is within the already established GTP, the PI has direct access to volunteers, staff, postdoctoral fellows, and other faculty involved in the broader research project and all resources, including computers, laboratory space, physiological equipment, and more. Additionally, there is a strong intellectual environment with many opportunities for building collaborations with junior and senior faculty at the GTP and within the Department of Psychiatry and Emory School of Medicine more broadly. **Brain Health Center (BHC):** Emory's BHC (https://www.emoryhealthcare.org/centers-programs/brain-health-center/index.html) combines the outpatient departments for psychiatry and behavioral sciences, rehabilitation medicine, neurology, neurosurgery, and sleep medicine to offer complete, coordinated care. Bringing these specialties together allows more than 400 researchers and clinicians from different specialties to work in collaboration to more rapidly predict, prevent, treat, or cure devastating diseases or disorders of the brain. The Emory Psychiatry & Behavioral Sciences provides patient-centered care for a full range of psychiatric and mental disorders, both an inpatient psychiatry program and a wide range of outpatient psychiatry services. Treatments include individual psychotherapy, electroconvulsive therapy, ketamine infusion therapy, and transcranial magnetic stimulation (TMS) and investigational trials in mood disorders. Both the Emory Veterans Program (Dr. Rothbaum, PI) and the Treatment Resistant Depression Program (Dr. McDonald) are located in the BHC. Drs. Kaslow, McDonald, and Rauch have offices at the BHC. Th PI has office space with a desk and computer within the Fuqua center for Late Life depression, which is located in the BHC and is directed by Dr. McDonald. TMS center: The TMS suite is located on the ground floor

of the BHC and can be easily accessed from the parking lot. The suite has a waiting room, locked closet for file storage and two large treatment rooms (132 sqft each). One treatment room is dedicated to research and the other room for clinical treatments. TMS is used clinically for treatment-resistant depression (about 6 patients a day) and there is an ongoing research study being with the Emory Veteran's Program (Barbara Rothbaum, PI). There is research space available in the research suite for conducting this study. **Center for Translational Research in Neuroimaging and Data Science (TReNDS):** TReNDS is a tri-institutional effort by Georgia State University, Georgia Institute of Technology and Emory University. The focus of the center is on developing, applying and sharing advanced analytic approaches and neuroinformatics tools that leverage advanced brain imaging. The goal is to translate these approaches into biomarkers that can help address relevant areas of brain health and disease. The underpinnings of the approach are large scale data sharing and multimodal data fusion techniques. The center provides a number of ways to facilitate knowledge transfer including seminars, hands-on workshops, semester long courses and informal project-based groups. The founding director is Dr. Vince Calhoun (co-mentor). The center is based at Georgia State University, a five-minute walk from the GTP offices. I will have access to a workspace with computing resources as well as neuroimaging analytic support from available technicians and post-doctoral researchers at all times.

- The GTP has an accumulating database of psychologically relevant referrals for any patient needs.
- All personnel will be trained and cleared by the PI for all research procedures, and their duties and functions. Regular meetings with all personnel involved in the study are being held. Additionally, the PI has two meetings per year with her whole mentor team to discuss the progress of the study.

25.0 Multi-Site Research when Emory is the Lead Site*N/A ☐

- N/A

26.0 References

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