Detailed Protocol
"Autonomic and fronto-cortical correlates of script-driven imagery of trauma-related nightmares compared with such imagery of index trauma in PTSD using ambulatory physiological and fNIRS recordings."
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BACKGROUND AND SIGNIFICANCE

Overview:
In those with posttraumatic stress disorder (PTSD), trauma-related nightmares are a hallmark re-experiencing symptom[1, 2] and a common and severe source of distress[3-8] often resulting in re-traumatization due to the lack of insight afforded by wakefulness. Proposed research will examine whether such nightmares might serve as targets for imaginal exposure during prolonged exposure therapy (PE), a first line treatment for PTSD. PE produces significant PTSD symptom reduction.[9] However, approximately 30% of patients prematurely drop out from PE treatment[10-16] and most still meet diagnostic criteria for PTSD at end of treatment.[12] Thus, means for increasing the efficacy of PE are important areas of investigation.[17-19] Fear extinction learning and memory are the neurocognitive underpinnings of PE.[17, 20] Because increased physiological arousal during PE can aid in extinction learning,[17, 21] recall of trauma-related nightmares might serve as an effective target for PE because of their greater immediacy and salience relative to the more temporally distant traumatic event. Our research group has developed standardized script-driven imagery (SDI) procedures whereby the degree of psychophysiological arousal induced by recollection of the traumatic event that precipitated posttraumatic symptoms (index trauma) can be assessed in those with PTSD.[22-25] A canonical variable for physiological reactivity to SDI (SDI-PR) is derived from skin conductance (SC), facial electromyography (EMG) and electrocardiography (ECG) and has served as a unitary, objective measure capable of distinguishing those with versus without clinician-diagnosed PTSD.[22, 26-29] Members of our team have also developed a novel ambulatory device, the NINscan, that can record SC, EMG and ECG along with simultaneous functional near-infrared spectroscopic (fNIRS) imaging of the lateral prefrontal cortex (LPFC).[30-32] fNIRS yields concentrations of oxygenated (O_2Hb) and deoxygenated (HHb) hemoglobin that can be used to assess cortical activation. Specific areas of the LPFC have been shown to activate and/or deactivate during SDI of an index trauma in persons with PTSD.[33] Notably, the LPFC includes the right inferior frontal gyrus (rIFG), a region shown to play a prominent role in inhibiting unwanted behavior and cognition,[34-37] in which reduced activation accompanies reduced inhibitory performance in persons with PTSD, compared to controls.[38, 39] In participants with PTSD and trauma-related nightmares, proposed research will compare psychophysiological responses and LPFC activation between SDI of a recent trauma-related nightmare versus SDI of the index trauma. During nights over a 2-week period, participants will audio-record time-stamped nightmare reports following all nightmare-induced awakenings. During two to four such nights, ambulatory polysomnography (PSG) will allow analysis of sleep physiology immediately preceding nightmare awakenings. A trauma-related nightmare report having sufficient length, clarity and resemblance to the index trauma will be selected and recorded as a script for SDI. The overarching goal of the proposed research will be to compare within-subject similarities and differences in brain and autonomic activation between imaginal replay of a trauma-related nightmare versus imaginal replay of the index trauma to determine the relative degree to which each evokes autonomic and frontocortical activations.

Significance:

Posttraumatic stress disorder (PTSD) is a major public health issue with lifetime prevalence estimates as high as 7.8%[40] and 12-month prevalence as high as 3.6%.[41, 42] Repetitive nightmares with content resembling an experienced trauma have been characterized as a highly specific "hallmark" symptom of PTSD.[2, 4, 5] **Trauma-related nightmares (TRNs)** are endorsed by as many as 50-70%[43,44] of individuals with PTSD, even when the traumatic event(s) occurred as long as 40 years previously.[45, 46] TRNs are highly correlated with more severe and persistent PTSD[47] and poorer overall sleep quality.[48, 49] TRNs disrupt sleep in at least two ways. First, they may produce anticipatory anxiety surrounding sleep and result in difficulty initiating sleep or sleep avoidance.[50] Second, they cause awakenings from sleep and acute physiological arousal that may make returning to sleep difficult.[48, 50] TRNs, insomnia, nocturnal panic attacks, night sweats, and simple and complex motor behaviors during sleep are especially common in combat veterans with PTSD.[51-54] These sleep disturbances, including TRNs, are often treatment resistant and contribute to poor treatment outcomes.[55] TRNs are linked to PTSD maintenance. For example, veterans who reported having nightmares had higher PTSD severity at both post-deployment baseline and at 6-month follow-up, at which time 41% of nightmare suffers continued to meet criteria for PTSD compared to less than 10% in those who did not experience nightmares.[47]

Increased physiological arousal during prolonged exposure therapy (PE) can facilitate extinction learning.[17, 21] Hence recall of TRNs might serve as an effective target for PE because of their greater immediacy and salience relative to the more temporally distant traumatic event. Enhancement of extinction learning by increased arousal is a documented phenomenon in experimental and clinical paradigms.[17, 21, 56-58] For example, sustained self-reported arousal during exposure therapy for Social Anxiety Disorder (SAD) predicted superior treatment outcome.[59] Similarly, enhanced exposure treatment for SAD has been reported with administration of Yohimbine, an alpha-2 agonist that increases noradrenergic neurotransmission and arousal.[60] In PE, the focus on "hot spots" is a naturalistic example of increasing arousal during exposure. Therapists typically direct patients to focus on "hot spots" after the initial recounting of the trauma from start to finish. Hence, we hypothesize that if trauma-nightmare SDI elevates responding above that produced by the index-trauma SDI, imaginal trauma-nightmare exposure could improve PE treatment outcome.

TRNs rarely occur in the sleep laboratory. Consequently, information on their physiological associates during sleep is limited and knowledge of their brain substrates is entirely lacking.[2, 3, 48, 54, 61-64] Although there have been laboratory and ambulatory studies in which TRNs were recorded using standard polysomnography (PSG),[44, 48, 54, 62, 63, 65] none have achieved a large sample or imaged brain activity. This motivates our proposed exploratory use of simultaneous PSG and functional near-infrared spectroscopic (fNIRS) imaging techniques. Although REM may be more conducive to the occurrence of TRNs,[2, 5, 62] a significant percentage can arise from NREM, especially N2.[44, 62, 63, 65-70] The two most successful attempts to record the physiology of TRNs used ambulatory PSG,[62, 63] one of which reported 57% of nightmares from REM and 37% from NREM sleep.[62] Arousals resulting in nightmare reports are often accompanied by sleep-disruptive events such as apneas, leg movements, startle-like arousals,[67] excessive body movements[68-71] and phasic sympathetic activation.[6, 52, 68]

Near-Infrared Neuromonitoring:

Human tissue is sufficiently transparent to near-infrared (NIR) wavelengths (650-950 nm) to enable non-invasive monitoring of brain oxygenation, perfusion, and neural activity.[30-32] By shining 2+ colors of NIR light on the scalp and placing a detector some distance away, the recorded signals can be used to measure concentrations of oxy-hemoglobin (O_2Hb), deoxy-hemoglobin (HHb), and total-hemoglobin (HbT, generally proportional to cerebral blood volume, CBV). We have validated NIRS sensitivity to functional changes in brain oxygenation against

simultaneous fMRI[72, 73] and others have since validated it against cerebral blood flow and volume.[74] Given multiple overlapping NIRS measurements, diffuse optical tomography (DOT) reconstruction techniques[30, 75-78] can be used to generate 2D or 3D images[79, 80] of the same cerebral variables, with spatial resolutions down to ~5 mm.[81] Temporal resolution can be upwards of 20 Hz.[82] The ability of fNIRS to image the brain is limited to the cortical mantle to a depth of ~10 mm.[83, 84] Consequently, the midline limbic structures such as the amygdala and ventromedial prefrontal cortex (vmPFC), hypothesized to be important to the generation of REM-sleep dreams, and especially their affective content,[7, 85, 86] cannot be imaged using fNIRS. However, dorsomedial PFC areas lying within ~10 mm of the surface of the cortical mantle, that have been inversely correlated with amygdala activity in PTSD patients,[87] could possibly be imaged using NINscan technology. Positron emission tomography (PET) studies have suggested that, during REM sleep, the lateral PFC (LPFC) remains in a deactivated state relative to wakefulness.[88-90] The relative deactivation of frontal areas may contribute to TRNs by withdrawal of top-down control of limbic structures.[6, 91, 92] Nevertheless, the lateral PFC is intimately involved in the regulation of emotion in the waking state.[93] To engage higher level emotion regulatory processes such as cognitive reappraisal, the lateral PFC may recruit more primitive paralimbic regions along with their associated functions such as fear extinction.[94] Specifically, the right inferior frontal gyrus (rIFG), a lateral region accessible to fNIRS imaging, has been uniquely implicated in domain-general inhibition (e.g., of action, cognition, emotion)[34-37] and impairment of its inhibitory function has been linked to PTSD.[38, 39] Activations and deactivations of the left and right IFG have been reported during script driven imagery (SDI) and PTSD symptom provocation paradigms.[33] The phenomenology of TRNs suggests a hyper-aroused state during which the dreamer may attempt to access resources to counter perceived fearful circumstances, which may provoke partial awakenings and hybrid sleep-wake states. Under such circumstances, frontal activity may increase. Alternatively, decreased lateral PFC activity may allow the intense midline and subcortical limbic activity presumably taking place during nightmares. In either case, the ability to visualize changes in blood flow across a broad region of the lateral PFC may yield important clues as to the neural mechanisms underlying this previously inaccessible phenomenon.

SPECIFIC AIMS

Specific Aim 1: Optimize standard operating procedures for using the NINscan device in our established SDI protocol as a flexible and portable alternative to previously employed laboratory-based hardware that lacked simultaneous fNIRS capacity."
Hypothesis 1: "NINscan will be easily optimized for SDI assessment in the MGH psychophysiology laboratory including event marking and systems for viewing incoming data in real time."
Specific Aim 2: Compare autonomic reactivity (SDI-PR) and fNIRS activation of the LPFC during SDI of the index trauma script and a trauma-related nightmare script.
Hypothesis 2: SDI-PR and LPFC activations during SDI of the trauma-nightmare script will exceed activations during SDI of the index-trauma.
Exploratory Aim 1: Determine whether the sleep stage immediately prior to trauma-nightmare awakenings and the trauma-nightmare content determine which individuals respond more to trauma-nightmare SDI or show a greater response to index-trauma SDI.
Exploratory hypothesis 1A: Individuals for whom the nightmare used to create their trauma-nightmare script was preceded, before awakening, by REM versus NREM sleep, will show greater SDI-PR and rIFG HbD responses to the trauma-nightmare script than to the index-trauma script.
Exploratory hypothesis 1B: Individuals for whom the trauma-nightmare script is judged most similar to the index trauma and/or the most severely stressful by 3 independent judges will show

greater SDI-PR and rIFG HbD responses to the nightmare script, compared to the index-trauma script.

INCLUSION/EXCLUSION CRITERIA

Phase 1

1. Age 18-60 years
2. Normal or corrected to normal visual acuity, normal hearing
3. Index event that meets DSM-5 PTSD stressor criterion A, *viz.* "The person was exposed to death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence" by direct exposure, witnessing in person, or having a close relative or friend exposed to violent or accidental actual or threatened death.
4. Self-report of at least 2 nightmares per week related to the index trauma. The trauma nightmares must contain veridical (vs., symbolic, interpreted, etc.) content that is reminiscent of the index trauma.
5. Individuals who meet criteria for at least three of the four DSM-5 criterion categories.

Phases 2 & 3

During the 2-week monitoring period (Phase 1), at least 4 recorded nightmares related to the index trauma with at least one suitable for creating a script for SDI.

Exclusion Criteria:

1. Lifetime history of psychosis, bipolar disorder, autism spectrum or other neurodevelopmental disorder, active risk to self or others
2. History of sleep apnea or an apnea/hypopnea index of >15 on the diagnostic night of ambulatory PSG (i.e., 15 or more sleep apnea-hypopneas per hour of sleep)
3. Neurologic conditions that could confound outcome variables, including past neurosurgical procedures, seizure, neurodegenerative disease, stroke, known structural brain lesion, significant head trauma with extended loss of consciousness and/or persistent neurological sequela (mild TBI allowed)
4. Medical conditions that could confound outcome variables such as severe cardiovascular or other systemic disease
5. Use of benzodiazepines, beta blockers, prazosin or antipsychotics (antidepressants or mood stabilizers with stable dose for ≥ 3 months allowed)
6. Current Alcohol and Substance Use Disorder or positive urine toxicology screen for drugs of abuse
7. MRI contraindications (e.g., metal in body or eyes, pacemaker, pump, stimulator, shunt, claustrophobia, weight >250 lbs.)
8. Pregnancy, breastfeeding or nursing: A pregnancy test (urine ß-HCG) will be conducted prior to the structural MRI for all women of child-bearing capacity
9. Supervisees of study investigators

SUBJECT ENROLLMENT AND SCREENING

Sampling Plan, recruitment, and retention strategies:

There are highly specific requirements for participants to begin Phase 1 and then to progress to Phases 2 and 3. Therefore, sampling will focus on identifying and retaining individuals with the

highest probability of generating usable nightmares. However, as noted above, in our sample we will aim for an equal proportion of men and women and an ethnic and racial composition reflecting the most recent Massachusetts census.

Recruitment

The recruitment target is for 50 participants (25 male and 25 female) to complete Phases 1-3 of the study. Withdrawals from the study will be replaced such that the targets for study completers are achieved. We will enroll 2-3 participants/month. Participants will be recruited through: the Boston Medical Center, the VA Boston Healthcare System specialty mental health clinics, the National Center for PTSD participant re-contact database, the Red Sox Foundation and Massachusetts General Hospital Home Base Program, outreach to military or first-responder organizations including our ongoing collaboration with the Boston Fire Department, and outreach to the general public (see below). Key personnel in this study provide access to PTSD patient populations at the above facilities. Specifically, our Consultant, Suzanne Pineles, Ph.D. is an investigator and Clinical Psychologist in the National Center for PTSD and is Assistant Professor in the Department of Psychiatry at Boston University School of Medicine (for which the Boston Medical Center serves as a teaching hospital) and Co-Investigator Kaloyan Tanev, MD is Medical Director of the Home Base Outpatient Clinic. Outreach to the general public will occur via internet bulletin boards, social media, MGH research participation websites (e.g., "Rally," "RSVP for health"), e-posting and physical postings at universities, re-contacting participants in past PTSD studies who have signed an agreement to be re-contacted (this is included in our consent forms). Notably, at the VA Boston Healthcare System alone, 6,448 male and 685 female Veterans with a documented PTSD diagnosis attended at least one appointment in FY2017. Based on our consultant Dr. Pineles' previous experiences recruiting participants with PTSD at the VA Boston Healthcare System, we anticipate no difficulty meeting our recruitment goal of 2-3 participants/month.

Retention

Any withdrawals from the study will be replaced such that a total of 50 study completers will be achieved. During the 14-day Phase 1 sleep-recording period, research staff will be in frequent contact with each participant. Participants will come to the Sleep and Anxiety Disorders lab to be instrumented for recordings on each evening prior to recording nights and they will also arrange with staff to return the equipment (usually on the following day). At each evening visit, participants will also meet with the PI or other clinical staff to complete the Columbia-Suicide Severity Rating Scale (C-SSRS)[95] via Zoom at which time they will be asked of any difficulties they have encountered with the study procedures and will be able to solve such problems with staff assistance. As in all of our studies, participants are encouraged to call the PI 24/7 with any concerns. For additional incentive to complete all study assessments, we offer a $100 bonus for completing the entire protocol.

When a candidate subject responds to an advertisement, they will be instructed to leave a phone number but remain anonymous until accepted into the first phase of the study. They will then be called and given a detailed description of the study. If they continue to be interested in participation, a phone screening will be conducted by one of the study investigators by a trained research assistant. Those not meeting inclusion/exclusion criteria or who choose not to participate will, therefore, remain anonymous. In the phone screening, major inclusion criteria will be confirmed and exclusion criteria ruled out based upon the candidate participant's self-report. Candidate participants' names, addresses and email addresses will be obtained if (and only if) they are determined to meet these initial inclusion/exclusion criteria and wish to participate.

STUDY PROCEDURES

Overview of protocol: The protocol consists of screenings followed by 3 experimental Phases. Individuals diagnosed with PTSD who report frequent TRNs will be recruited from the MGH-Red Sox Foundation's Home Base program, the Boston VA Medical Center, local hospital trauma clinics, and from the community. Interested individuals will first complete a telephone screening followed by a series of structured clinical interviews using a Zoom Healthcare Secure Room to diagnose PTSD and comorbid psychiatric disorders, confirm initial inclusion criteria, rule out exclusion criteria and create an audio-recorded account of their index trauma. Participants passing screenings will then proceed to **Phase 1** and complete 2 weeks of at-home sleep and nightmare diaries and time-stamped audio-recorded reports of dream content upon awakening from any nightmare. They will also wear a wrist actigraph throughout this period, complete two to four nights of ambulatory PSG, and complete on-line questionnaires. Nightmare data will be examined for frequency and thematic similarity of nightmares to a participant's reported index trauma. Those reporting at least 4 such nightmares with at least one that is clearly related to the index trauma and sufficiently detailed for script creation will be invited to participate in **Phase 2**. Phase 2 participants will undergo a structural MRI scan and will then be scheduled to undergo MRI-guided positioning of fNIRS sources and optodes using the BrainSight2 System. **Phase 3**. Participants' nightmare and index trauma reports will be audio-recorded for use as scripts during SDI. The participant will then undergo two SDI sessions on a single day, one with a nightmare script and one with an index-trauma script, during which they will wear the NINscan. Sessions will be separated by 1 hour and counterbalanced across participants for script order.

Informed Consent:
When a candidate subject responds to an advertisement, they will be instructed to leave a phone number but remain anonymous until accepted into the first phase of the study. They will then be called and given a detailed description of the study. If they continue to be interested in participation, a phone screening will be conducted by a trained post-doctoral fellow or research assistant. Those not meeting inclusion/exclusion criteria or who choose not to participate will, therefore, remain anonymous.

During the phone screening, major inclusion criteria will be confirmed and exclusion criteria ruled out based upon the candidate participant's self-report. Candidate participants' names, addresses and email addresses will be obtained only when they are determined to meet these initial inclusion/exclusion criteria. They will then be scheduled for a visit to MGH to sign a consent form, complete questionnaires, be given the C-SSRS, and provide a hand-written account of their trauma as well as a urine toxicology sample. The day before the subject comes to MGH to sign consent they will be sent a copy of the consent form via email so that they may read it ahead of signing.

They will then come to MGH to provide written informed consent, complete a urine toxicology screen, fill out the Life Events Checklist (LEC-5), fill out the PCL-5, provide a hand-written account of their trauma, and will be paid an additional $30. No minors or other individuals unable to provide informed consent will be recruited. All individuals invited to the interview will undergo the entire interview. Those excluded or placed on a waiting list will be paid $50 for their time.

Screening: Participant candidates will first complete a telephone screening for the inclusion and exclusion criteria detailed in "Protection of Human Subjects" and summarized below. Those passing telephone screening will undergo psychiatric and sleep disorders interviews using the

Structured Clinical Interview for DSM-5, Research Version (SCID-5-RV)[96] and the Clinical Interview for DSM-5 Sleep Disorders Module (SCISD),[97] and screened for suicidality using the Columbia-Suicide Severity Rating Scale (C-SSRS).[95] They will then be screened for PTSD symptomatology with the CAPS-5, PCL-5, Childhood Trauma Questionnaire (CTQ),[98] Trauma History Questionnaire (THQ),[99] Life Events Checklist for DSM-5 (LEC-5)[100] and Peri-traumatic Distress Inventory (PDI).[101] Phase 1 inclusion criteria will be a SCID-5-RV-based diagnosis of PTSD and self-report of at least 2 nightmares per week related to a specific "index trauma" that contains veridical content reminiscent of the index trauma. Phase 2 and 3 criteria will be at least 4 audio-recorded, time-stamped nightmares related to the index trauma during the 14 nights of Phase 1 with at least one that is suitable for SDI.

Phase 1: Participants accepted to Phase 1 will give an audio-recorded narrative of the index trauma for later SDI. They will then receive an actiwatch, a voice-activated, time-stamping digital audio-recorder, a list of bodily sensations that they might experience during nightmares, and copies of the Evening/Morning Sleep Questionnaire (EMSQ) diary.[102, 103] All nightmares resulting in awakenings will be recorded at the time of awakening. Participants will be instructed to depress the actiwatch event marker when they awaken and when they complete recording and to estimate the subjective duration of the nightmare. Audio-recorded nightmare reports will be compared, by study staff, with the audio-recorded narrative account of the index trauma. Participants will also complete a battery of questionnaires, remotely, and two to four nights of ambulatory PSG using the Somte-PSG ambulatory recorder (Compumedics USA, Inc., Charlotte, NC). The first night will screen for sleep disorders and acclimate participants to PSG. Participants who do not record 4+ TRNs one of which is suitable for SDI during Phase 1 will be debriefed, paid for portions of the study completed and discharged.

Phase 2: Participants will undergo a structural T1 MPRAGE MRI scan. This will be used along with the BrainSight Frameless Stereotactic System (Rogue Research, Inc., Montreal, CN) to localize fNIRS optodes at 8 bilateral regions of interest (ROIs) (4 per hemisphere) including the frontopolar cortex (BA 10), as well as superior (BA 9), middle (BA 46) and inferior (BA 47) frontal gyri.

Phase 3: When we capture a suitable nightmare from a participant, the recorded nightmare report will be transcribed and audio-recorded by an investigator as a TRN script following our standard procedures.[28] Participants will then come to the laboratory and complete 2 SDI sessions with NINscan monitoring, one of which will use the script derived from the TRN and the other the script derived from the index trauma. Presentation order of the scripts derived from the TRN and from the index trauma will be counterbalanced across participants. Because PTSD symptomatology and extinction memory may vary with the menstrual cycle,[104-106] female participants not on oral contraceptives will undergo SDI during the early follicular phase of their cycle.

Script Driven Imagery: Adapting standardized SDI protocols,[22, 26-28] scripts will be created from audio-recorded accounts of the index trauma about which a participant's TRNs represent a re-experiencing. The audio-recorded report and list of bodily sensations experienced from an awakening during Phase 1 will provide material for the nightmare script. Account of a second personalized stressful event unrelated to the index traumatic event will be similarly recorded as well as one recording each of a recalled positive and emotionally neutral experience. These accounts will be transcribed and the subject will clarify and expand on details as necessary. Scripts approximately 30 sec in duration will then be composed and recorded by experienced staff, portraying each experience in the second person, present tense. Six 30-sec standard generic scripts of both neutral and emotional situations (2 each of neutral, fearful and positive

experiences) will also be recorded. Script recordings will be played to participants through headphones as they vividly imagine each event and physiological data are continuously sampled.

Processing of fNIRS signal: Accelerometry data will be used to identify any head motions during the measurement periods. The 25-Hz optical data (raw-background) will be digitally low pass filtered at 5Hz followed by application of the modified Beer-Lambert Law[107] per channel, following our previous work.[108] This will provide continuous measures of O_2Hb, HHb, and HbT concentrations relative to resting baseline.

PSG measures: Sleep measures obtained from ambulatory PSG will include amounts of each sleep-stage (N1, N2, N3, REM) as a percent of total sleep time (TST) and spectral power in 7 frequency bands within each sleep stage. REM-specific measures include REM latency, REM fragmentation,[109] REM rapid eye movement density (REMD),[110] REM power in the theta (4-7Hz) frequency (REMtheta),[111] and heart rate variability during REM.[112, 113] On the diagnostic night, pulse-oximeter, respiration transducers, nasal cannula and tibialis channels will be added to screen for OSA and periodic limb movement disorder. Any participant showing 10+ apneas or hypopneas/h or >15 leg movements with arousals/h, will be withdrawn and referred to a sleep clinic. An experienced research PSG technician will score sleep using AASM criteria.[114, 115] NINscan-based PSG measures will be scored as in our previous work[108, 116, 117] using the same criteria.[114, 115]

Structural MRI: images will be acquired with a 32-channel head coil in a 3T Siemens Prisma scanner using automated scout and shimming and high-resolution 3D T1 MPRAGE sequences (TR/TE 1,2,3,4/flip angle = 2530ms/1.69, 3.55, 5.41, 7.27ms/7°) with an in-plane resolution and slice thickness of 1.0 mm.

Targeting ROIs using BrainSight Frameless Stereotactic System: The BrainSight system enables real-time visualization of probe locations relative to a subject's previously acquired structural MRI image allowing precise, unobtrusive placement of optical probes with respect to underlying anatomy. The device can be used to non-invasively and accurately locate fNIRS optodes on a subject's scalp over specific cortical areas. We will visualize 100 mm^2 circular ROIs (approximately 8, 10mm-diameter fNIRS voxels) centered on specific MNI coordinates in each subject in order to ensure imaging approximately the same LPFC areas across subjects.

Actigraphy and sleep diary: The waterproof Actiwatch 2 (Philips Respironics, Bend, OR) is worn on the non-dominant wrist 24h/day[118, 119] and counts arm movements in 1-min epochs. Participants press an event marker when beginning to attempt sleep and when waking for the day. Epochs are scored as sleep or wake using a standardized algorithm. The EMSQ[102, 103] queries daytime activities and the time one begins attempting sleep (evening), and wake time, subjective sleep latency, total sleep time, and number of awakenings (morning).

Self-report assessments: A secure online MGH system will obtain the: 1.) Pittsburgh Sleep Quality Index [120] with PTSD addendum;[121] 2.) Insomnia Severity Index;[122] 3.) Morningness-Eveningness questionnaire;[123] 4.) Spielberger State-Trait Anxiety Inventory;[124] and 5.) Inventory of Depressive Symptomatology.[125]

Outcome and predictor variables: For Hypothesis 2, outcomes will be "difference scores" between biosignals from the 30-s trauma-related epoch of the nightmare and index-trauma SDI and their baseline epochs (30 s of silence preceding the respective script).[22, 26-28] For fNIRS, the quantities used to compute difference scores will be O_2Hb minus HHb concentrations (HbD)[30, 72]

at each ROI. Peripheral outcome will be SDI-PR[22, 26-28] computed from HR, SC and EMG responses to the index trauma and nightmare scripts. Primary outcome of Exploratory Hypotheses 1A and 1B will be whether or not SDI-PR and HbD are larger in response to trauma-nightmare SDI than to index trauma SDI. Predictor variables for Exploratory Hypothesis 1A will be sleep stage prior to awakening from trauma nightmare. Predictor variables for Exploratory Hypothesis 1B will be ratings by 3 judges, blind to all other participant data, on two 7-point Likert-type scales of 1) the degree of similarity between each individual's index-trauma and trauma-nightmare scripts, and 2) the emotional severity of the recorded trauma-nightmare experience.

Statistical analyses: As feasibility assessments of NINscan methodology, Hypothesis 1 The qualitative optimization of NINscan's biosensor configuration, biosignal acquisition, event marking, and interface with software delivering SDI stimuli, rather than quantitative hypothesis testing, is the focus of Aim 1. To test Hypothesis 2, the two **primary outcome variables** (rIFG fNIRS HbD and SDI-PR) will be compared between trauma-nightmare and index-trauma SDI using multiple regression adjusting for age, sex and duration since trauma. **Secondary outcome variables** (HbD from the 7 remaining fNIRS ROIs) will be compared between groups using the same regression model as for the primary fNIRS outcomes adjusting for multiple comparisons using the false discovery rate.[126] Analysis of Exploratory Hypothesis 1A: We will investigate whether a stronger response to the trauma-nightmare as compared to the index-trauma script is associated with REM sleep using logistic regression, with REM sleep (0/1), sex (M/F) and duration since trauma as predictors. Analysis of Exploratory Hypothesis 1B: The similarity between the trauma-nightmare and index-trauma scripts and the severity of the trauma-nightmare script will be evaluated for each subject by 3 judges using 7-point Likert scales. The relationship between these evaluations and a greater SDI-PR or rIFG HbD response to trauma-nightmare than index-trauma SDI will be assessed using ordinal regression, with sex, judge ID, and duration since trauma as additional covariates.

Power analysis: For the primary outcome in Aim 2, we will compare physiological response and fNIRS in the rLIFC between scripts for the index trauma and the associated nightmare in each of 40 subjects completing the study (i.e., dropouts will be replaced). Based on a paired t-test at the 0.05/2 two-tailed significance level (adjusting for the two outcome measures), we will have 80% power to detect an effect size of d=0.50. In order to power the hypothesis in Exploratory Aim 1, we first assume that each of 50 subjects have one nightmare and that 60% of these nightmares will occur during REM sleep.[62] For this situation, we will have 80% power to detect whether the probability of having greater SDI-PR or rIFG HbD response to the trauma-nightmare, compared to the index-trauma script is 0.70 or greater for patients who had nightmares during REM sleep, and 0.30 or less for those whose nightmares were not during REM sleep, based on Fisher's exact test, at the 0.05 two-tailed significance level.

POTENTIAL RISKS AND PROTECTION FROM RISKS

Risks of self-report during clinical screening, completing questionnaires and recording nightmares:
Participants may feel uncomfortable or embarrassed revealing psychological information during clinical interviews and when completing questionnaires. Interviews and questionnaires may also induce negative emotional reactions due to the reactivation of trauma-related memories. For the same reason, dictating dream reports following awakenings from nightmares may induce or

exacerbate trauma-related negative emotional reactions. The protections from these risks that we implement are detailed below.

Risks from script-driven imagery (SDI) procedures:
Risks from the SDI procedure primarily include negative emotional reactions to the reactivation of trauma-related memories. There is a chance that recalling one's traumatic memories could worsen PTSD symptoms. However, we regard this as unlikely for two reasons. First, subjects with PTSD repeatedly experience traumatic memory reactivations as a feature of the disorder. Second, we have reactivated traumatic memories in hundreds of PTSD subjects during more than 30 years' experience with the script preparation procedure and have found few instances of symptomatic exacerbation. The protections from these risks that we implement are detailed below.

Risks from NIRS and NINscan monitoring:
NIRS is an investigational tool in regular use for over 40 years. Although no adverse effects have been reported, it is possible that effects not yet reported may occur. If lasers like those in the device are shone directly into the eye, eye injury could potentially occur. NIRS monitoring requires coupling sensors to the skin on the scalp. This is achieved by fastening the sensors to a pad or cap, placing it over the head, and holding it in place with a head or chin strap. Positioning the sensors may require parting the hair and will require making secure contact with the skin. It is possible that skin irritation could occur beneath sensors. The study team has received extensive training on the psychophysiological procedures and this will minimize discomfort from the application of the electrodes.

Risks from ambulatory polysomnography:
The removal of some of the sleep recording electrodes and sensors placed with tape may pull slightly on exposed skin and feel like a band-aid being removed. Participants may feel this sensation despite our use of tapes and materials specially designed for people's skin. Participants may not sleep as well as usual when wearing ambulatory PSG equipment. As a result they may be sleep deprived and feel tired in the morning.

Risks from structural MRI:
Although MRI is thought to be hazard free, some subjects may find the enclosed space of the scanner to be physically uncomfortable or anxiety-producing. Every effort will be made to reassure the patient and minimize any discomforts while in the fMRI scanner. Subjects will be able to converse with a staff member via a microphone and speaker system. Every effort will be made to reassure the patient and minimize any such discomforts. Noise from the scanner can also cause discomfort. To reduce the discomfort caused by loud noises, subjects will wear earplugs that minimize ambient scanner noise while still allowing communication with staff. Subjects may ask to have a scan stopped and discontinue participation in the study at any time.

Unexpected Findings:
As NIRS is not a clinical measurement, it is possible, but unlikely, that we could find a clinical abnormality in healthy participants. Unexpected findings may also occur during the structural MRI.

Accidental data release:
There is a small possibility of an inadvertent release of a subject's data with identifiable information, as with any electronic data.

Protection Against Risks

Written informed consent will be obtained from each subject. Subjects can request that a study be stopped at any time during their participation.

Repeated safety assessments:
We will conduct careful screening to identify individuals at higher risk for developing suicidal ideation, for example those with a history of active suicidal ideation or attempt and those with current suicidal ideation. Such individuals will not be enrolled in the study and appropriate clinical care and referrals will be provided. Either Dr. Lasko or Dr. Pace-Schott (a Massachusetts Licensed Mental Health Counselor) will use Zoom to administer the C-SSRS[95] at every visit to MGH which include the initial psychiatric and sleep interviews, the two to four visits for PSG instrumentation, and the day of SDI testing. At every visit, there will be a licensed clinician present to provide assistance as well as a licensed clinical psychologist or psychiatrist on call. If a participant endorses any of the C-SSRS queries concerning suicidal ideation, intent or plan, they will be assessed by the licensed clinician investigator present who will then consult with one of the two psychiatrist co-investigators on our protocol (Kaloyan Tanev, MD and John W. Winkelman, MD, PhD). Minimally, the participant will be instructed on how to contact MGH's Acute Psychiatry Service (APS), which provides emergent psychiatric care on a 24-hour/day basis for individuals in the Massachusetts area. We also provide a complete listing of emergency mental health services in Boston. However, if acute suicidality or other psychiatric distress is detected while a participant is enrolled in the protocol, we will accompany them to the MGH Emergency Department and remain with them until they are evaluated by health care providers or emergency services. If a participant develops suicidal ideation outside of study visits they will have the PI's number that can be called 24/7 and he will advise them to immediately go to the nearest emergency room and facilitate their doing so by identifying local resources. If the participant is homicidal, MGH hospital security will be called and standard procedures for addressing such issues at MGH will be followed.

Clinical screening:
Because trauma history is being evaluated, we expect a degree of emotional distress during the screening sessions. The risk of an increase in symptoms during screening will be discussed during the informed consent process. If an adverse emotional reaction occurs during screening, a psychologist (Drs. Lasko or Pineles), psychiatrist (Drs. Tanev or Winkelman) or a Licensed Mental Health Counselor (Dr. Pace-Schott, the PI) will be available for guidance and intervention, including making referrals to initiate or supplement treatment, carrying out the emergency procedures detailed above and/or withdrawing the participant from the study.

Home-based nightmare reporting:
Should a severe emotional reaction occur during nightmare reporting, participants will be instructed first to go to the nearest emergency room. They can also contact the PI, Dr. Pace-Schott, a Licensed Mental Health Counselor (LMHC), 24h/day, 7 days per week and he can also provide guidance. If nightmare recording elicits persisting distress during the following day(s), the above noted clinicians will be available for guidance and intervention, including making referrals to initiate or supplement treatment, carrying out the emergency procedures detailed above and/or withdrawing the participant from the study. We will further protect participants by reminding them that they are free to withdraw from the study at any point.

Script-driven imagery:
We will seek to protect participants from the emotional distress that might be aroused by the SDI procedure in the following ways. Only investigators and highly trained research assistants

will conduct the SDI procedure. If an adverse emotional reaction occurs during SDI, a psychologist (Drs. Lasko or Pineles), psychiatrist (Drs. Tanev or Winkelman) or a Licensed Mental Health Counselor (Dr. Pace-Schott, the PI) will be available for guidance and intervention, including making referrals to initiate or supplement treatment, carrying out the emergency procedures detailed above and/or withdrawing the participant from the study. Participants will be reminded at each study visit that they are free to withdraw from the study at any point. There is also a chance that recalling one's traumatic memories could worsen PTSD symptoms. However, we regard this as unlikely for two reasons. First, subjects with PTSD repeatedly experience traumatic memory reactivations as a feature of the disorder. Using SDI, we have reactivated traumatic memories in hundreds of PTSD subjects during more than 30 years' experience with the script preparation procedure and have found few instances of symptomatic exacerbation. As noted above, all participants will be assessed for suicidal ideation at every study visit including the SDI sessions.

Ambulatory polysomnography:
All subjects will be told that sleeping when wearing ambulatory PSG equipment, especially after the first night, can result in some sleep loss and resultant daytime sleepiness. They will be cautioned not to drive or operate dangerous machinery until they determine that they are fully alert. After being instrumented for ambulatory Somte-PSG recording during Phase 1, participants who have come by public transportation will be given taxi vouchers to return home. Free parking will be provided for those who drive. The PI is on call 24 hours a day, 7 days per week, to address any participant concerns throughout the study.

Near-Infrared Spectroscopy:
NIR light delivery by our NINscan system will be well below the Maximum Permissible Exposure (MPE) level for long-duration (8 h) exposures, which is the ANSI limit for light delivery at these wavelengths. Moreover, the CW-NIRS light sources are diffused and diverge in a wide angle (>50 deg) at the probe end because of a diffusing filter affixed over the light source. This results in a Nominal Ocular Hazard Distance (NOHD) of less than 5 cm, which is lower than the 10 cm focusing distance of the retina. Hence, the NIRS measurements do not necessitate eye protection.

MRI:
A pregnancy test (urine ß-HCG) will be conducted prior to the structural MRI for all women of child-bearing capacity; a positive test will preclude scanning. Three levels of screening for metallic objects on or inside the body are completed prior to MRI scanning session. First, participants are queried during the initial telephone screening and anyone with a pacemaker, medication pump, vagal stimulator, deep brain stimulator, TENS unit, ventriculo-peritoneal shunt or any other introduced metal such as shrapnel are disqualified. Second, before the anatomical scanning session, each participant must complete the Martinos Center Patient/Volunteer Screening Form. An affirmative answer to most items on this form disqualifies the participant. A few items (e.g., tattoos), however, may be brought to the attention of the Martinos Center MRI managers who alone can determine whether or not this participant can be scanned. Third, participants must pass through a ferrous metal detector before entering the MRI environment. The Martinos Center for Biomedical Imaging has clearly written and posted safety protocols designed for all contingencies associated with MRI scanning and the MRI environment. This includes a protocol for rapidly contacting emergency first responders. All research staff who participate in MRI scanning at the Martinos Center must have completed MRI safety training. In addition, a Martinos Center Certified MRI Scanner must be present at all scanning sessions and 2 such individuals must be present on evenings, weekends and holidays. A certified scanner must have participated in regular Martinos Center scanning sessions as a trainee for at least 4

months and must pass an examination administered by one of the MRI center managers. The PI and all current research assistants are Certified MRI Scanners.

Unexpected Findings:
Although MRI and fNIRS scans associated with this protocol are for research purposes only, an MGH radiologist is available for consultation whenever a brain anomaly is noted. If necessary, the radiologist will inform the participant of the finding and offer to communicate that information to their physician of choice (e.g., primary care or specialist) for follow-up.

Data Protection:
All study staff will be trained on the importance of confidentiality. All research staff must have successfully completed the Collaborative Institutional Training Initiative (CITI) basic training for biomedical researchers as well as periodic refresher trainings. All data will be coded with a random alphanumeric subject code, unrelated to the participant's name, initials, or dates related to their participation. All research data will be labeled with this code only, and the mapping between patient and code will be kept in an encrypted and password-protected location accessible only by the study investigators and the research coordinator. Only the PI and requisite co-investigators will have access to the subject's personal data.

POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO HUMAN SUBJECTS AND OTHERS

Benefit to subject:

It is anticipated that most subjects will not derive direct benefit from participation in the study. However, participants will be referred, if desired, to appropriate clinical services should any serious psychopathology be noted during clinical psychiatric screenings, any sleep disorder noted during the clinical sleep interview or the acclimation/sleep disorder screening night or if any anomaly is noted on their structural MRI. In addition, if desired by the participant, referrals can be made for treatment of PTSD at any point before, during or after the study. The investigators are well positioned to make such referrals given their extensive network of clinician colleagues at MGH and other Boston area hospitals. There will be no costs incurred by the subject as a participant in planned procedures.

Importance of the knowledge to be gained:

During PE for PTSD, trauma-related nightmares might offer targets for exposure treatments that are of greater immediacy and salience than the more temporally distant index trauma that originally precipitated an individual's PTSD. As such, use of trauma-related nightmares might strengthen arousal during PE and thereby enhance therapeutic extinction leading to greater reductions in PTSD symptoms. The proposed research will provide preliminary evidence as to whether or not this is the case by comparing both autonomic and brain responses to script-driven imagery of the original traumatic experience to script-driven imagery of a recent trauma-related nightmare. Additionally, the ability to assess activity in the LPFC during SDI might provide crucial information relating to individual differences in treatment response. For example, greater engagement of the LPFC following transcranial magnetic stimulation has been shown to predict treatment outcome from PE in PTSD.[127] Moreover, the Phase-4 participants will provide the first glimpse into LPFC activity during nightmares, and could generate hypotheses on potential methods to assess treatments of nightmares (pharmacological or behavioral) in naturalistic settings.

Compensation:

Participants will be paid up to a maximum of $475 for completion of Phases 1-3 of the study. This amount is in line with our standard practice. Partial completion of the study will be compensated on the following schedule.

$30 for in-person visit to MGH to sign consent and perform urine toxicology screen.
$70 for completing on-line clinical interviews
$150 for completing Phase 1 of the study (14 days of audio-recording of experienced nightmares, nightmare and sleep diaries, actigraphy, 2-4 ambulatory PSG nights, online questionnaires)
$125 for completing the 2 script-driven imagery procedures and positioning of fNIRS optodes
$100 bonus for completing entire protocol

Participants will be informed that they will be discontinued in the study if: (a) if at the clinical interviews they do not meet study criteria, (b) if they produce a positive urine toxicology screen after signing consent, (c) if they produce a positive pregnancy test at the structural MRI, (d) if a sleep disorder is detected on the diagnostic night of ambulatory PSG, (e) if an insufficient number TRNs are obtained during Phase 1. However, they will be compensated in full for the activities they have completed based upon the schedule above.

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Questionnaires

Psychiatric Interview:
- Structured Clinical Interview for DSM-5, Research Version (SCID-5-RV)
- Clinician Administered PTSD Scale for DSM-5 (CAPS-5; past month version)
- Life Events Checklist (LEC-5; standard self-report)
- PTSD Checklist for DSM-5 (PCL-5)

Sleep Interview:

- Clinical Interview for DSM-5 Sleep Disorders Module (SCISD)
- Cover pages for SCISD

REDCap Questionnaires
- Pittsburg Sleep Quality Index (PSQI)
- Pittsburg Sleep Quality Index addendum for PTSD (PSQI – PTSD addendum)
- Epworth Sleepiness Scale (ESS)
- Morningness-Eveningness Questionnaire (MEQ)
- Insomnia Severity Scale (ISI)
- Spielberger Trait Anxiety Inventory (STAI – Trait)
- Revised NEO Personality Inventory (NEO-PI-R)
- Peritraumatic Distress Inventory (PDI)
- Quick Inventory of Depressive Symptomatology – Self-report (QIDS-SR)
- Childhood Trauma Questionnaire (CTQ)

Questionnaires given before and after script-driven imagery
- Stanford Sleepiness Scale (SSS)
- Spielberger State Anxiety Inventory (STAI- State)
- The Positive And Negative Affect Schedule – Mood Scale (PANAS)