Protocol Title: Dopamine Enhancement of Fear Extinction Learning in PTSD (1R21MH108753)

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A. Benefit to Society and Purpose

Current state-of-the art treatments for posttraumatic stress disorder (PTSD) are lacking in efficacy. There are two main evidence-based psychological treatments for PTSD. Prolonged Exposure (Foa et al. 1991) (PE) is a largely-exposure based intervention that has been found efficacious for the reduction of PTSD symptoms (Foa, Rothbaum, Riggs, & Murdock 1991; Schnurr et al. 2007); however, PE is associated with post-treatment remission rates of only ~53-60% (Foa et al. 1999; Resick et al. 2002; Schnurr, Friedman, Engel, Foa, Shea, Chow, Resick, Thurston, Orsillo, Haug, Turner, & Bernardy 2007). Cognitive Processing Therapy (CPT) (Resick and Schnicke 1992) is also a widely studied and efficacious psychological treatment for PTSD, which focuses both on exposure to the trauma memory as well as cognitive therapy techniques. As with PE, post-treatment remission rates for CPT are only ~53-60% (Monson et al. 2006; Resick, Nishith, Weaver, Astin, & Feuer 2002; Resick et al. 2008) thus also indicating need for improvement in overall efficacy and consistency of response across individuals.

Repeated exposure to the trauma memory (RETM) in a safe context is a therapeutic intervention common to both PE and CPT (though implemented differently in PE and CPT). RETM is based on a fear extinction model (Foa, Rothbaum, Riggs, & Murdock 1991; Foa and Kozak 1986; Rothbaum and Davis 2003): the memory of the trauma is conceptualized as a conditioned stimulus (CS+) that triggers anxiety responses (conditioned responses) due to its association with the traumatic event (i.e., the unconditioned stimulus). Repeated exposure to the traumatic memory (CS+) in a safe context is theorized to weaken the predictive value of the CS+ and thereby weaken the ability of the traumatic memory or reminders to elicit marked distress.

Extensive research on the neural mechanisms mediating fear extinction suggests that fear extinction is mediated largely by the functional interaction between three separate neural structures (Milad et al. 2007; Myers and Davis 2007; Phelps et al. 2004; Sotres-Bayon et al. 2006). First, the amygdala is critical for the detection of the CS+ and motivating the expression of fear-relevant behavioral responding. Second, the hippocampus is involved in contextual modulation of amygdala processing in the presence of the CS+. Third, the medial prefrontal cortex (mPFC) has direct anatomical projections to the amygdala (Ghashghaei et al. 2007) and is critical for down-regulation of amygdala response. Finally, these neural mechanisms mediating fear extinction overlap with the neural circuitry known to be altered in PTSD (Rauch et al. 2006; Shin et al. 2006).

Basic research also demonstrates that fear extinction learning involves formation of a new memory, not the erasure of an old memory (Bouton 2002; Bouton 2004; Craske et al. 2008; Craske et al. 2014) . Fear responding during subsequent presentations of the CS+ is determined by the degree of competition between the new (safe) memory and the old (danger) memory. For example, context renewal refers to recovered fear responding after fear extinction learning by placing the organism in a different context than where the extinction learning occurred (Bouton 2002; Bouton 2004). Thus, efforts have been devoted to enhancing the consolidation of the new (safe) memory (Davis et al. 2006; Walker and Davis 1997) in order to

boost its subsequent recall across contexts and thereby decrease fear responding upon future presentations of the CS+ in new contexts.

There is emerging research demonstrating that dopamine is critical to the consolidation and subsequent recall of fear extinction learning (Abraham et al. 2012; Haaker et al. 2013a; Hikind and Maroun 2008; Mueller et al. 2010). Rodent studies have demonstrated that dopamine antagonists delivered after fear extinction training lead to *increased* fear responding upon subsequent CS+ presentation, and that dopamine agonists delivered after fear extinction training lead to *decreased* fear responding upon subsequent CS+ presentations. Similarly, a recent study of healthy adult humans demonstrated that oral administration of 150 mg L-DOPA after fear extinction learning led to decreased fear responding, even when tested in a new context[31]. Further, this study also found that resting-state functional connectivity, measured ~45 minutes after post-extinction learning L-DOPA administration, between the ventral tegmental area (VTA) and mPFC was correlated with magnitude of mPFC recruitment during recall of the fear extinction learning. This latter finding suggests that the mechanism by which L-DOPA boosts consolidation of fear extinction learning is through acutely reorganized dopaminergic resting-state networks. Indeed, other studies have demonstrated an acute effect of L-DOPA administration on resting-state functional connectivity within dopaminergic neural networks (Cole et al. 2013a; Cole et al. 2013b; Kelly et al. 2009). Thus, agents that increase dopamine transmission acutely during the post-extinction learning consolidation window, and thereby acutely altering organization of dopaminergic neural networks, show promise for boosting the consolidation of fear extinction memories and decreasing fear responding.
It is well established that dopamine neurotransmission demonstrates a nonlinear inverted “U” shaped relationship with measures of performance (Cools and D'Esposito 2011). This line of research demonstrates an optimal level of dopamine neurotransmission, varying by the task, for achieving optimal performance. Similarly, human studies using L-DOPA demonstrate an inverted “U” shaped relationship between L-DOPA dose and measures of performance (Monte-Silva et al. 2010; Thirugnanasambandam et al. 2011).

Genetic variation is a primary contributor to individual differences in baseline dopamine neurotransmission (Cools & D'Esposito 2011; Frank and Fossella 2011). Individuals with specific alleles in genes coding for high baseline dopamine demonstrate better performance on tasks probing working memory, cognitive control, and social cognition (Diamond et al. 2004; Egan et al. 2001; Meyer-Lindenberg et al. 2005). Genetic variants in baseline dopamine neurotransmission would therefore be expected to modulate performance-enhancing effects of L-DOPA, such that individuals with low endogenous would be expected to have increased performance upon exogenously increasing dopamine neurotransmission; whereas individuals with high endogenous dopamine would be expected to have performance deteriorate from exogenously increasing dopamine neurotransmission. In support of this hypothesis, a recent study found an interaction between L-DOPA administration and endogenous dopamine neurotransmission (as indicated by a polygenic score pooled across COMT, DAT, DRD1-3) on motor learning performance, such that individuals with a combination of alleles coding for higher baseline dopamine demonstrated a weaker learning benefit from L-DOPA, whereas individuals

with a combination of alleles coding for lower baseline dopamine demonstrated a stronger learning benefit from L-DOPA (Pearson-Fuhrhop et al. 2013). These data demonstrate the non-linear relationship between performance and dopamine levels, suggesting that any investigation of potential effects of boosting dopamine neurotransmission as a means of boosting learning needs to account for baseline dopamine neurotransmission.

Overall, the proposed project seeks to demonstrate the engagement of post-extinction dopamine neurotransmission and downstream acute reorganization of dopaminergic resting-state neural networks as a means of increasing consolidation of generic fear extinction learning in adult women with PTSD.

B. Specific Aims

Specific Aim 1: Test the degree to which endogeneous and exogeneous manipulations of dopamine neurotransmission affect fear extinction learning across multiple indices. *Hypothesis:* L-DOPA dose will interact with dopaminergic gene score to predict fear extinction learning across indices.

Specific Aim 2: Test the degree to which post-extinction functional connectivity within dopaminergic neural networks mediates the effect of dopaminergic manipulation on fear extinction learning. *Hypothesis*: The L-DOPA x dopaminergic gene score will predict enhanced post-extinction dopaminergic functional connectivity, which in turn predicts enhanced fear extinction recall.

C. Study Design

Overview. There are three main stages to this experimental protocol: 1) Assessment, 2) Day 1 fMRI, and 3) Day 2 fMRI. Participants would complete these stages across 2-3 days, depending on participant need. Day 1 fMRI and Day 2 fMRI will always be consecutive days.

During the Assessment stage, participants would undergo a structured clinical interview to assess trauma history and mental health diagnoses (See Assessments Section).The assessment stage lasts 3-4 hours.

During Day 1 fMRI, participants would complete ~40 min fMRI scan, then ingest a pill (placebo, 100mg L-DOPA, or 200 mg L-DOPA) upon leaving the scanner and wait in a waiting room for ~45 minutes. Participants then complete the Side Effect Checklist to assess for any drug-related side effects. The participant would then undergo a 7 min resting-state fMRI scan, which concludes Day 1 fMRI. Day 2 fMRI lasts about 2 hours.

Participants return ~24 hours later for Day 2 fMRI, in which they first complete the Side Effect Checklist again and then complete a single ~40 minue fMRI scan. Day 2 fMRI lasts about 1 hour.

Study Population

Participant recruitment. Participants will include 105 women aged 21-50. In order to achieve these enrollment goals, up to 260 adults could be recruited and screened for eligibility. Participants will be recruited primarily from the WisPIC outpatient mental health clinic where the PI maintains a clinical practice. We will also recruit through focused community networking with women's shelters and related service organizations and through community-wide general advertisements (e.g., newspaper ads, flyers, etc). We have worked with women's shelters in the past by contacting them to notify them of the study and providing brochures, which then they post in their facility. Interested participants would then contact us to learn more about the study.

Inclusion/Exclusion Criteria. Inclusion criteria will be 1) females age 21 – 50 years of age, 2) a current diagnosis of PTSD where the index traumatic event includes physical or sexual assault, 3) English speaking, and 4) medically healthy. Assault exposure will be defined as witnessed or directly experienced exposure to physical or sexual assault (Cisler et al. 2011; Kilpatrick et al. 2000; Kilpatrick et al. 2003; Resnick et al. 1993)[1, 59]. To facilitate generalization to real-world populations of women with assault-related PTSD (Kessler et al. 1995; Kessler 2000), current comorbid major depressive disorder or anxiety disorders will not be exclusionary as long as the PTSD diagnosis is primary.

Exclusionary criteria include: 1) internal ferromagnetic objects (such as electronic devices, surgical implants, shrapnel, etc.), 2) major medical disorders (such as cancer), 3) ADHD, 4) psychotic disorders, 5) mental retardation, 6) developmental disorders, 7) active substance use disorders, 8) pregnancy, and 9) glaucoma. Medications will not be exclusionary, as long as the medication has been stable for at least 4 weeks and do not effect neurovascular properties upon which BOLD fMRI capitalizes (e.g., water pills). Acute sedatives / pain killers (e.g., benzodiazepines, vicodin) and prescription stimulants (e.g., Adderall) would not be permitted for 6 hours prior to the scan or for two hours after the scan. Medication prescription use will be modeled as a covariate. See below for detailed exclusion criteria.

Due to safety concerns, participants with these conditions will be ineligible to participate:

- Claustrophobia, or the inability to lie still in a confined space
- Major medical disorders (e.g., HIV, cancer)
- Magnetic metallic implants (such as screws, pins, shrapnel remnants, aneurysm clips, artificial heart valves, inner ear (cochlear) implants, artificial joints, and vascular stents), as these may heat, pull, or twist in the strong magnetic field of the MRI scanner
- Electronic or magnetic implants, such as pacemakers, as these may stop working
- Permanent makeup or tattoos with metallic dyes
- A positive pregnancy test (for females), since the effect of strong magnetic fields on the developing fetus remains unknown and inconclusive. (We will conduct a pregnancy test for all female participants of childbearing potential on the day of the MRI scan. Participants who test positive would be notified of this positive result)
- A self-reported history of loss of consciousness (greater than 10 minutes)
- Physical disabilities that prohibit task performance (such as blindness or deafness)

- Psychotic disorders (e.g., schizophrenia)
- Any other condition that the investigator believes might put the participant at risk

Due to their effects on image quality, participants with the following MAY be ineligible to participate per Principal Investigator's judgment:

- Medications which may affect image quality (e.g., water pills)
- Nonremovable dental implants, such as braces or upper permanent retainers, as these will distort the MRI images we collect (note: filings, crowns, and silver or gold teeth are OK)
- Any other condition, medication, or implant that the investigator believes would degrade image quality or render data unusable

Phone screening.
Initial assessment will occur in two phases. First, a phone screening will be conducted to ensure a high probability that participants are eligible for the study. The phone screening begings with a description of the study and phone screening and obtaining verbal consent to continue with the phone screen. This phone screening will assess the presence of assault exposure, PTSD symptoms, and transportation capability to WISPIC. The phone screening will also assess other possible exclusionary criteria such as medical disorders, internal metal, nonremovable dental implants, permanent makeup or tattoos with metallic dyes, history of loss of consciousness, claustrophobia, and any other conditions the investigator believes might put the participant at risk. If the participant meets probable inclusion criteria, the research coordinator will schedule the participant for phase-two of the assessment process. For clinic participants, this phone screening might be done in person.

Informed Consent Process. The participant will first be given a written and verbal description of the study and informed consent. The PI or designated staff will discuss the informed consent form with the subject volunteer. The consent process will take place in a quiet and private room. Subjects may take as much time as needed to make a decision about their trial participation and may take the document home if desired. The person obtaining consent will thoroughly explain each element of the document and outline the risks and benefits, alternate treatment(s), and follow-up requirements of the study. Participation privacy will be maintained and questions regarding participation will be answered. No coercion or undue influence will be used in the consent process. No research related procedures will be performed prior to obtaining informed consent. All signatures and dates will be obtained. A copy of the signed consent will be given to the participant. The informed consent process will be documented in each subject's research record.

Participant assessment.

Participants will complete several interviews, questionnaires, and neurocognitive tests to determine psychological and medical history, current life functioning, history of drug use, stress

experiences, individual traits, family functioning, and demographic variables. The first visit will be ~3-4 hours, during which they will complete the bulk of these measures and all interviews. Based on time, some of the questionnaires will be administered after the second MRI.

We hope to recruit participants from this study to participate in additional studies in our lab. To reduce overall burden on the participants, we would like to be able to use some of these participants' assessment data from this study for the new study (2017-0736). We will include a line in the informed consent document describing this use of the participant's data from this study and allowing the participant to provide informed consent to use their data for the additional study. All self-report and neurocognitive measures would be shared between the two studies. Structured clinical interview data would also be shared between the two studies, with the exception of the Clinician Administered PTSD Scale (CAPS), which will be re-administered in the new study to assess for current PTSD symtpoms. If there is sufficient blood and saliva left over that could be shared with the other study as well, if not new blood / saliva samples woud be collected. Participants who do not wish to have their data used from the current study would undergo all new assessments if they participate in the new study.

Structured clinical inteviews:
Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I): measures current psychological functioning and drug use history (First et al., 2002).

Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II) Borderline Personality Disorder Module: measures prevalence of symptoms related to the presence of borderline personality disorder (First et al., 2002).

Clinician Administered PTSD Scale (CAPS): Is the gold-standard structured interview to diagnosis PTSD and characterize symptom severity.

National Women Survey Trauma Assessment (NSA): assesses assaultive event exposure and other types of childhood adversity history and chronology (Kilpatrick, et al. 2000, Kilpatrick, et al. 2003; Resnick et al., 1993).

Columbia Suicide Severity Rating Scale (CSSRS): measures the severity of current suicidal ideation.

The structured clinical interview diagnostic assessments (SCID, CAPS) would be delivered by research staff and audiorecorded, with a random 20% selected for reliability checks. The clinical interviews are audiorecorded for the purpose of data quality assurance: we would conduct interrater reliability on randomly selected 20% of the interviews. The audiorecordings would be acquired with a digital recorder and the electronic files are stored according to participant ID (no identifying information) on a password protected computer that only study personnel have access to. After the interrater reliability has been assessed, we would delete the audiorecordings.

Self-Report Measures:

These measures will be administered via an iPad linked to UW's secure REDCAP database system.

Data Collection Form: internal form used to collect study specific information such as handedness, age, race/ethnicity, medications, etc.

Beck Depression Inventory (BDI): measures the severity of current depression (Beck et al., 1961).

Childhood Trauma Questionnaire (CTQ): measures histories of abuse and neglect during childhood (Bernstein, et al. 2003).

Difficulty in Emotion Regulation Scale(DERS): assesses multiple aspects of emotion dysregulation (Gratz & Roemer, 2004).

Five Facet Mindfulness Questionnaire (FFMQ): assesses the level of awareness over the inner experience (Baer et al., 2006).

Mood and Anxiety Symptoms Questionnaire (MASQ): measures general (non-disorder specific) symptoms of mood dysfuncation and anxiety.

Menstrual Cycle Information Log: charts the length and regularity of the menstrual cycle and type and dosage of any birth control medications.

Pittsburgh Sleep Quality Index (PSQI): measure of the quality of sleep in the past month.

Positive and Negative Affect Scale (PANAS): measure of current (at this moment) affect (Watson et al., 1988).

Posttraumatic Stress Disorder Checklist- 5 (PCL-5): assesses the 20 DSM-5 symptoms of PTSD (Weather et al., 2013).

Electrotactile Stimulation Calibration: Explains and assess the targeted intensity of stimulation. Note: this measure is completed during fMRI scanning.

Side Effect Checklist: asssesses possible side effects across multiple domains of functioning.

Neurocognitive measures:
One-word receptive vocabulary test (Brownell, 2000): a well-normed measure of verbal IQ.

Digit span subscale of WAIS-IV: measures working memory capacity.

Spatial cueing task: the spatial cueing task (e.g., Cisler et al., 2010) is a computer-administered protocol in which a stimulus picture (fear facial expression or neutral facial expression) is presented as a cue on either the left side of a computer screen, whose offset either predicts or does not predict the subsequent location of a response probe. There are 132 trials distributed evenly across the following factorial design: 2 (cue type: fear face vs neutral face) x 3 (cue position: opposite to probe, same as probe, center of screen). Each trial lasts 500 ms plus the participants reaction time.

Reinforcement learning task: The fear extinction protocol (see below) requires the tracking of associations between stimuli; thus, as a control for generic reinforcement learning, we would have participants complete a reinforcement learning task outside of the scanner. Similar to our other protocol (2016-1307), the task would resemble commonly used decision-making tasks towards the goal of earning as many points as possible. Participants select geometric shapes that are associated with a pre-determined probably of earning or losing points. Additionally, as a distractor, each of the shapes is associated with the appearance of a picture selected from the International Affective Picture System (IAPS), a well-normed and widely used set of pictures. Shapes would be associated with the occurrence of either a negative (e.g., snakes) or neutral (e.g., mountains) picture, as determined by the normed ratings of the IAPS. The points would displayed concurrently with the picture, but have no relationship to the amount of points earned. There would be ~150 trials and the task would take ~8 minutes to complete.

Mock MRI scan

During session 1 or session 2, subjects may go to the MRI Simulator room for a mock scan session. In addition, if the subject is particularly anxious, we may ask him/her to participate in an additional mock scan between sessions 1 and 2.

In the lab, the mock scanning room has been designed to very closely enact a neuroimaging procedure with the exception that the scanning apparatus is not capable of generating a magnetic field. The mock scan protocol is critical for the current study, primarily to decrease the novelty of the experimental procedures, which is especially important for patients with anxiety. Importantly, it also allows for a practice session prior to data collection. The participants will hear an audio file that replicates the scanner noise that occurs during the real scanning session. The subject will be able to see images through goggles or a mirror that are similar to those they will see during the actual scan. Study personnel will support and coach subjects if they have any difficulties accommodating to the scanner environment. During this mock practice session the importance of keeping the head still during the scan is emphasized, and participants have a chance to practice this.

MRI Procedures

Before the MRI scan, participants will be given an explanation of the study's procedures and screened with the MRI Safety Screening Form for metal objects and claustrophobia. The participant will then lie supine in the scanner. Participants will wear ear plugs and noise-

cancelling headphones for communication and view visual stimuli through a mirror attached to the imaging head coil. Participants will undergo an anatomic scan in order to acclimate to the MRI environment. The order of the tasks will be counterbalanced.

All participants will be asked to leave a urine sample prior to the scan. The sample would be tested for tobacco and drugs of abuse as well as to confirm lack of pregnancy. Heart rate, respiration, and galvanic skin response will be measured during the scan using the BIOPAC physiology monitoring system. A plethsmograph (rubber band) placed around the subject's fingernail will measure heart rate via changes in blood oxygenation beneath the cuticle. A flexible respiration transducer (rubber belt) around the subject's abdomen will measure expansions and contractions as the subject breathes. Electrodes placed upon the subject's skin will measure galvanic skin response.

Generic fear conditioning and extinction task. This fMRI task (Haaker, Gaburro, Sah, Gartmann, Lonsdorf, Meier, Singewald, Pape, Morellini, & Kalisch 2013a; Phelps, Delgado, Nearing, & LeDoux 2004) is divided into three distinct phases: fear acquisition, fear extinction, and recall. The unconditioned stimulus (UCS) would be an electrotactile stimulation delivered to the left wrist using our MRI compatible BIOPAC equipment. The intensity of the stimulation would be set prior to the experiment for each participant as a level that is "unpleasant but not painful," a procedure that is commonly used in the literature (Haaker et al. 2013b; Phelps, Delgado, Nearing, & LeDoux 2004). Participants would use the Electrotactile Stimulation Calibration form to rate the degree of unpleasantness.

In the fear acquisition phase, participants would be presented, in an alternating fashion, with two geometric shapes (triangle and circle) for 3 s duration (3-6 s ITI). One shape would be the CS+ whose offset overlaps (at 2.5 s) with presentation of the UCS with a 50% probability. The other shape would be the CS- and never paired with the UCS. The fear conditioning phase would occur in Context A (with the target stimuli presented against a yellow background).

The fear extinction phase would occur in Context B (with the target stimuli presented against a blue background), during which the CS+ is no longer followed by the UCS. The shapes and background would be counterbalanced as CS+, CS-, Context A, and Context B.

The recall phase occurs ~24 hours later on Day 2, during which participants are presented with the CS+ and CS- alternating between Contexts A and B in a pseudorandom manner, and no presentations of the UCS. The alternation between the contexts allows for testing resistance to context renewal of the fear memory. Every fourth trial, participants also provide self-report ratings of the anxiety elicited from the CS+ and CS- and expectation of the UCS following each CS using a Likert Scale of 0-10. In each phase, there are 12 presentations of the CS+ and CS-.

Resting task. The connectivity of the mesolimbic dopaminergic system will be investigated using a standard resting state task, in which participants lie passively in the scanner for 7 minutes and are simply told to let their mind wander freely.

Characterization of Endogenous Dopamine Neurotransmission and Genetic Analysis. Following prior studies (Monte-Silva, Liebetanz, Grundey, Paulus, & Nitsche 2010; Pearson-Fuhrhop, Minton, Acevedo, Shahbaba, & Cramer 2013), we would characterize endogenous dopamine neurotransmission via a combined gene score across the following genes: COMT (rs4680), DAT (rs28363170), DRD1 (rs4532), DRD2 (rs1800497), and DRD3 (rs6280). Catechol-o-methyltranferase (COMT) is a catecholamine degrading enzyme. A val^{158}met polymorphism (rs4680) results in ~4 times less enzyme activity and therefore higher baseline dopamine levels. Dopamine transporter protein (DAT) removes synaptic dopamine. The 9-repeat allele of the DAT gene (rs28363170) is associated with less DAT protein and accordingly greater synaptic dopamine levels. DRD1-3 are dopamine receptors. The DRD1 gene has an A/G SNP (rs4532), where the G allele is associated with increased dopamine levels. The DRD2 gene has a polymorphism characterized by a Glu to Lys substitution (rs1800497) that results in ~40% reduction in D2 receptors and reduced D2 binding. The DRD3 gene has a Ser to Gly substitution (rs6280) associated with higher affinity to dopamine. Consistent with prior studies, the presence of COMT val^{158}met allele, DAT 9-repeat allele, DRD1 G allele, DRD2 Glu allele, and DRD3 Gly allele would all be coded = 1, with other allele presentations coded = 0. Thus, an individual's gene score would be the sum across the 5 genes, creating a range of 0 (lowest endogenous dopamine) to 5 (highest endogenous dopamine). Prior studies using these gene combinations to characterize endogenous dopamine neurotransmission have found additive associations with motor learning and depression symptoms (Monte-Silva, Liebetanz, Grundey, Paulus, & Nitsche 2010; Pearson-Fuhrhop, Minton, Acevedo, Shahbaba, & Cramer 2013). Genes coding dopaminergic function (COMT, DAT, DRD2) have also been implicated in PTSD (Cornelis et al. 2010; Wolf et al. 2014).

Participants would provide blood samples, from which DNA will be extracted from whole blood using the Qiagen Biorobot M48 according to standardized protocols. Single nucleotide polymorphisms (SNPs), such as those in *COMT*, will be genotyped in 384-well format using validated Taqman assays and the 7900 Sequence detection system (ABI). Variable number tandem repeat polymorphisms (VNTRs), such as those in *SLC6A3 (aka DAT1)*, will be genotyped using established assays from the literature (Fuke, Suo, Takahashi, Koike, Sasagawa, & Ishiura, 2001). This assay involves PCR amplification of the region in each subject followed by size discrimination using standard electrophoresis or an Applied Biosystems 3100 genetic analyzer. All variants will be tested for adherence to Hardy-Weinberg Equilibrium, and those that do not will be excluded from further analyses. Approximately, 10 mL of blood will be collected for analysis in standard purple-top vials. In the event an inadequate amount of blood or poor sample is collected, all participants will also provide a saliva sample (approximately 2mL) for genotyping if necessary.

Clinical Trial Procedures

L-DOPA

Administration. Prior to pill ingestion, participants would undergo a standardized medical exam (see attached physician screening form) with a study physician to rule out medical and pharmacological contraindications for L-DOPA prescription.Upon passing the medical exam, the study physician would write a prescription to the UW research pharmacy, who maintains the blind, to dispense to our research staff the correct pill. Participants would be randomized to receive either a placebo, 100mg (with 25 mg carbidopa to inhibit peripheral decarboxylase), or 200mg (with 50 mg carbidopa to inhibit peripheral decarboxylase) pill of L-DOPA (see below for randomization and blinding procedures).

The study drug is prepared and maintained by the research pharmacy. Medication is put into two gel capsules, which are identical across the dose ranges of placebo, 100mg and 200mg. Medication kits are prepared separately for the three groups and stored in the locked nurses office of WisPIC along with the study logs of drug administration and allocation for each subject (e.g., subject 001, allocated to group 'blue', provided dose on 2/18/17). There is no washout period required for this study, though participants are required to have been stable on previous medications for at least 4 weeks. Use of MAO-I in past two weeks is exclusionary. As noted above, physician evalulation is performed prior to prescription being written. Participants are assessed for side-effects after 40-min and again 24-hours later.

Justification and Rationale for L-DOPA Dose Choices. The dose of 100 mg is consistent with prior studies of L-DOPA on learning as a dose optimizing the inverted U-shaped curve for the dopamine/performance relationship, while the dose of 200 mg is chosen as a suprathreshold dose that establishes the upper bound of the inverted U curve of the dopamine/performance relationship (Monte-Silva, Liebetanz, Grundey, Paulus, & Nitsche 2010;Thirugnanasambandam, Grundey, Paulus, & Nitsche 2011). We chose 200 mg as the supratheshold dose, as opposed to 300 mg or 500 mg, in order to keep the dose small enough to not inadvertently break the blind (i.e., higher L-DOPA doses are more likely to result in side effects such as dizziness, nausea, fatigue, etc.), and 200 mg has been successfully used in prior learning studies as a suprathreshold dose.

Double Blind Clinical Trial Methodology. Neither participants nor research staff would know which pill (placebo, 100 mg L-DOPA, or 200 mg L-DOPA) is given to participants. Instead, for tracking and balanced randomization reasons, groups would be labeled as either "blue", "red", or "yellow", with only a staff member at the UW pharmacy filling the study prescriptions knowing which label received which pill. This pharmacy staff member would have no interaction with the participants.

Balanced Randomization. To ensure randomization results in placebo and drug groups balanced on key variables that might affect treatment response, participants would be assigned to treatment conditions through "urn" randomization, which was developed and utilized in previous trials, using Microsoft Access program (Kosten et al. 2003; Oliveto et al. 2011; Poling

et al. 2006). In urn randomization, an algorithm modifies ongoing randomization probabilities based on prior composition of treatment groups, maximizing multivariate equivalence of treatment groups (Wei and Lachin 1988). Thus, urn randomization offers the benefits of balancing allocation of important prognostic variables in treatment groups while still retaining the benefits of random assignment (Stout et al. 1994). Participants will be randomized based on comorbid diagnoses, age, and current medication usage.

Implementation. The "urn" randomization will be implemented by a department statistician, who will have no direct contact with the participants and no knowledge of the pill assignment to the group labels and thus has negligible chance of biasing the randomization sequence or implementation.

Blind Assessors. The clinical research coordinators performing the assessments will be blind to the treatment conditions; thus minimizing the possibility of systematically biasing the assessment procedures.

Study Compensation

Participants will be compensated for their time and participation. They will receive $60 for the assessment phase, $70 for Day 1 fMRI, and $80 for Day 2 fMRI. Participants will also receive $15 for travel to each of the scheduled appointments, up to 3 visits ($45). WISPIC and HERI will not be held responsible for replacing lost or stolen checks. Participants may elect to be picked up and transported to the Health Emotions Research Institute through Union Cab at no cost to them.

On-Going Data Collection at the University of Arkansas for Medical Sciences (UAMS).
This study is additionally enrolling participants at UAMS. Upon completion of data collection, only coded data would be merged across the two sites. That is, participants' data across the sites would be combined into a dataset using only a unique study ID for each subject, and only the site at which the data was collected would be able to link that study ID to the individual participant's PHI. De-identified behavioral data and imaging data would be transferred between sites via SSH on encrypted and firewalled network servers (MRI-APP2.heri.psychiatry.wisc.edu and PRIrocks.ad.uams.edu).

Sharing DNA samples for sequencing and analysis.
DNA samples will be shared with Dr. Elizabeth Binder and the Max Planck Institute for the purposes of sequencing and analysis. Given Dr. Binder's expertise in PTSD and genetics, she will be a collaborator on subsequent manuscripts describing results from this study.

D. Data and Safety Monitoring

See separately uploaded Data and Safety Monitoring document.

E. Risks and Benefits

Potential risks

Internal metal during MRI scanning. One potential safety concern is participant internal metal during MRI scanning, which can be dangerous and possibly even lethal. Ferrous metals may exhibit torque or deflection forces while in the presence of the static and gradient magnetic field. Nonferrous metals may absorb radio-frequency (RF) energy during pulse sequences that may cause heating of the metal.

Possible Peripheral Nerve Stimulation (PNS). Due the large amount of RF energy emitted during scanning, PNS may occur if certain tissues absorb this energy, manifesting as muscle contractions.

Possible hearing damage resulting from scanner noise. Another possible risk involved with scanning is the loud noise of the scanner. While collecting data, the machine may emit sounds at decibel levels high enough to result in hearing damage or loss.

Electrotactile stimulation during MRI scan. The risk of electrotactile stimulation includes discomfort, unpleasant sensations, and possibly pain.

Assessment of mental health and traumatic event exposure. One potential psychological risk of the proposed study is the possibility that some participants might experience distress or become offended when asked questions pertaining to victimization and mental health history. Nevertheless, there is a specific protocol, should a participant become distressed as a result of participation in this study. This is discussed in detail below.

Assessment of suicidal ideation. During the clinical interview in the depression module and the CSSRS, questions regarding suicidal ideation are asked. This may elicit distress from participants; however, there is a specific protocol should a participant report suicidal ideation, intent, or plan, and a protocol to decrease distress, described below.

Transient distress in relation to the imaging task. Another potential risk is that the imaging procedure will elicit anxiety/distress. Participants are able to quit the task at any time by indicating to the technician that they wish to do so. Participants have a call button during the imaging session that allows them to indicate to the technician at any time that they wish to stop.

Personal health information/Loss of confidentiality. With all research participation, there is a risk that personal information obtained from research participants will be mishandled, and confidentiality may be compromised. With the current vulnerable sample of assaulted women, an associated risk of confidentiality loss is that the abuser might learn of their participation in this study and possibly then retaliate. An additional confidentiality concern is suicidality; that is, if suicidal ideation is observed, it might be clinically indicated to break confidentiality to protect the participants. Additionally, as mandated reporters, if we learn about a situation the participant is involved pertaining to child abuse or elderly abuse, we may have to break confidentiality. Upon IRB approval, we will apply for a certificate of confidentiality.

Side effects from acute administration of L-DOPA. It is possible that acute administration of L-dopa can cause transient side effects, such as dizziness, nausea, headaches, and drowsiness.

Blood draw and genetic testing. The risks associated with the blood draw itself include discomfort or bruising at the draw site. Because genetic analysis involves information that may uniquely identify participants, there is a risk of genetic information being used to re-identify participants.

Adequacy of protection against risks. Procedures to minimize risks identified in the previous section are outlined below.

Internal metal during MRI scanning. Participants will be verbally screened several times prior to MRI scanning in order to exclude any participants with internal metal.

Possible Peripheral Nerve Stimulation (PNS). All pulse sequences will be conducted with specific absorption rates of <36% in order to reduce the possibility of PNS. Participants will be instructed to notify the study team if they notice any involuntary muscle contractions.

Possible hearing damage resulting from scanner noise. All participants will be required to wear ear plugs and noise-canceling headphones to prevent any damage to their hearing.

Electrotactile stimulation. Each participant will have the ability (with the assistance of study staff) to calibrate how intense the stimulation is prior to being scanned. Participants will be instructed to select a stimulation level that is “maximally uncomfortable, but in no way painful”. Participants will know exactly what the stimulation will feel like prior to entering the scanner. Additionally, once the participant has been placed in the scanner, prior to beginning the task, they will be asked to confirm their chosen stimulation level. Participants will also be reminded that they may stop the scan at any point if they become uncomfortable.

Assessment of traumatic event exposure: Given the vulnerability of the sample, the women will be told that they do not have to answer any questions they do not want to, and that they can withdraw their participant or take a break whenever they want to. Additionally, the trauma assessment interview (from the National Women Survey) is worded with dichotomous questions so that the participant only has to answer yes or no to a series of questions. In our pilot testing with over 70 adult women, we had no adverse events or withdrawals from the study during the trauma assessment. Additionally, if in ascertaining a participant’s current condition, the need for clinical intervention is determined, the appropriate mental health referral will be arranged.

Procedures for suicidal participants. Individuals who are actively suicidal, defined as intending to hurt or kill themselves in the acute time frame, will receive immediate crisis counseling services by the UW psychiatrist on call for such emergencies. The treatment response may include hospitalization. These participants will be ineligible for the experimental sessions.

Transient distress in relation to imaging task. With regard to potentials risks regarding anxiety/distress during imaging, as noted above, the participants are able to quit the tasks at any time using an emergency call button. Participants who wish to terminate early due to distress will be assessed by a clinical psychologist (the PI or the postdoctoral fellow) and appropriate recommendations will be made (e.g., for individual therapy, instruction on coping and affect reduction skills, etc).

Personal health information/Loss of confidentiality. Standard practices will be used to protect participant confidentiality and personal health information, including removing identifiers from all data collected, using only numbers to identify participant data, and keeping all data files when not in use in a locked filing cabinet behind a locked office. No names or other identifiers will be used in computerized data files.

Furthermore, some women may participate who are currently in an abusive relationship. In cases such as this, it is sometimes possible that the abuser would become angry and retaliate against the participant for disclosing the abuse. In to protect the participant against possible retaliation from the abuser, we would assess the current safety of the participant with respect to the perpetrator. This clinical assessment would be conducted a female research staff member. Depending on participant need given their unique circumstance, an individualized safety plan would be created for the participant that might include entering therapy, withdrawing participation, entering a women's shelter, contacting the police, etc.

Participants would be notified in the informed consent that confidentiality might be breached in the case of suicidal ideation in order to protect the participant's safety.

Side effects from acute administration of L-DOPA. To ensure the participants protection, we escort the participant to a waiting room for monitoring for ~45 minutes after drug administration. We then administer a standardized medication Side Effect Checklist to assess for any side effects that require immediate attention. Upon return to the lab 24 hours later, we re-administer the Side Effect Checklist to assess for any new side effects that require attention prior to beginning the fMRI Day 2 procedures. Participants are additionally given a 24-hour emergency contact number in case of any study-related emergencies.

Side effects of a single low dose of L-DOPA are minimal and might include transient dizziness, nausea, or a general feeling of discomfort. Should these side effects be observed, we would 1) remind participants that these side effects are common and short lasting, 2) tell them they can request to speak with a study's physician if they wish, 3) escort them to the UW ER if they request, or if it is clinically indicated, that they should receive immediate attention. Participants who are unable to continue with the study procedures due to side effects (e.g., not able to complete the resting-state scan 4~5 minutes after pill ingestion) would be removed from the study after following the necessary and indicated clinical procedures (e.g., escorting to ER if necessary, consulting with the study physician, referring to psychiatric treatment as indicated, etc).

Blood draw and genetic analysis. To minimize any discomfort during blood draw, only study staff trained to perform blood draw will be allowed to collect the sample from the participant. To protect the identity of research participants and prevent them from being re-identify, all samples sent for analysis will be de-identified. In addition, genetic analysis will be limited to a handful of genes related to the production and movement of dopamine in the brain. This will also minimize the psychological and social risks associated with genetic analysis. Only a few genes will tested and participants are not re-contacted on the basis of their results.

F. Benefits to Subjects

Potential benefits of the proposed research to the subjects and others. We do not expect participation in this study to benefit the individual participant directly. However, if the study is successful, the knowledge gained could lead to improvements in treatment efficacy, which would have a major beneficial impact on others. This information is conveyed to participants in the informed consent.

Importance of the knowledge to be gained. This application aims to test the hypothesis that facilitated dopamine neurotransmission boosts efficacy of fear extinction learning in PTSD. Knowledge gained from this study would critically inform current leading models of fear extinction learning as well as models of exposure therapy for PTSD. Consequently, it is expected that knowledge gained from this study would then lead to improved therapy modalities, which would have a significant impact on societal public health.

G. Statistical Plan

*Power Analyses and Targeted Sample Size***.** A prior study using a fear extinction methodology among healthy humans found significant effects of L-DOPA using an N of 20 in each drug group (Haaker, Gaburro, Sah, Gartmann, Lonsdorf, Meier, Singewald, Pape, Morellini, & Kalisch 2013a); the prior dopamine gene score x L-DOPA study found a significant interaction using an N of 25 for the two drug groups. Prior studies examining the effect of L-DOPA on resting-state FC have used sample sizes of < 20 per cell (Cole, Beckmann, Oei, Both, van Gerven, & Rombouts 2013a; Cole, Oei, Soeter, Both, van Gerven, Rombouts, & Beckmann 2013b; Kelly, de, Di, Copland, Reiss, Klein, Castellanos, Milham, & McMahon 2009). Using GPower software to estimate power, a sample size of 35 per drug group (total N = 105) would provide power > .9 to detect large effects and power ~.8 to detect medium-large effects.

Data analysis.

Primary Analytic Framework for Fear Extinction Effects. The overall data analysis framework for Aim 1 fear extinction analyses consists of a 3 (group: placebo vs 100 mg L-DOPA vs 200 mg L-DOPA) x 2 (cue: CS+ vs CS-) x 2 (context: A [learning context] vs B [extinction context]) x 6 (dopamine gene score: 0 [low endogenous dopamine] – 5 [high endogenous dopamine]) mixed design focused on Day 2 fear responding. Preliminary analyses would test for any baseline

differences in fear responding or extinction learning on Day 1 and include these variables as covariates if needed. Analyses would also control for ancestory as well as other demographic or clinical variables should they differ between groups.

Neural circuit ROI definition and extraction. The neural circuit indices would be 6 *a priori* regions of interest (ROI) with anatomical coordinates defined from the recent literature (Delgado et al. 2008; Haaker, Gaburro, Sah, Gartmann, Lonsdorf, Meier, Singewald, Pape, Morellini, & Kalisch 2013a; Milad, Wright, Orr, Pitman, Quirk, & Rauch 2007; Phelps, Delgado, Nearing, & LeDoux 2004; Schiller et al. 2008) and include bilateral amygdala, bilateral hippocampus, ventromedial PFC, dorsal anterior cingulate cortex. Following standard preprocessing, first-level analyses conducted for each individual separately would consist of whole-brain GLMs, in which the task design (CS+ vs CS- during Context A vs B) is modeled as boxcar events convolved with a canonical HRF. The task design is regressed onto each voxel's timecourse within a GLM framework and using restricted maximum likelihood to account for serial correlation, resulting in a whole-brain spatial map indicating the degree to which each voxel responds to CS+ vs CS- during Context A vs B. The mean contrast values for CS+ vs CS- as a function of context is then extracted from the voxels within 6 mm spherical ROIs for the six ROIs. These analyses would provide six (for each ROI) indices of activation, calculated separately for each participant, that would be used in multivariate analysis of variance (MANOVA) analyses to define the impact of L-DOPA and dopamine gene score on consolidation of fear extinction learning.

Planned Fear Extinction Analyses: We would conduct three sets of MANOVA analyses, one with the set of Day 2 neural circuit indices (amygdala, dorsal anterior cingulate cortex, caudate) as dependent variables, one with the set of Day 2 physiological indices (SCR, HR, HRV) as dependent variables, and one with the set of Day 2 verbal/self-report indices (anxiety, UCS expectation) as dependent variables. In these analyses, the mixed effects of L-DOPA group, dopamine gene score, cue, context, and the interactions are entered as factors explaining variance in the multivariate combination of the set of dependent variables. Interactions with context would demonstrate the effect of the manipulations on robustness to context renewal effects. Additionally, any factors that differ between groups, such as Day 1 fear responding, age, or comorbid diagnoses, would also be entered as covariates should the balanced "urn" randomization fail. Given the three sets of tests, FDR correction (Benjamini and Hochberg 1995) would be used to control for alpha inflation. If the multivariate analyses reveal significant between-group differences in our measures of neural, psychophysiological and/or verbal/self-report, they would be followed up with simple effect testing to identify the specific conditions and measures driving the larger multivariate effect. We would additionally test for linear and quadratic contrasts for the group comparisons in order to establish dose-dependent learning, and its gating by dopamine gene score, effects on these primary DVs. All analyses would be completed prior to breaking the blind in order to minimize bias.

Defining dopaminergic resting-state functional connectivity (FC). Following the prior studies cited above(Haaker, Gaburro, Sah, Gartmann, Lonsdorf, Meier, Singewald, Pape, Morellini, & Kalisch 2013a;Kelly, de, Di, Copland, Reiss, Klein, Castellanos, Milham, & McMahon 2009), we

would define three regions-of-interest (ROIs) with which to calculate resting-state FC: 1) the substantia nigra/ventral tegmental area (SN/VTA; MNI X, Y, Z coordinates = -8, -18, -20 mm), a critical region of the dopaminergic midbrain, 2) the dorsal caudate (DC; MNI X,Y,Z coordinates = ±13, 15, 19 mm), and the ventral (limbic) striatum (VS; MINI X,Y,Z coordinates = ± 16, 12, -10 mm). Consistent with our prior RSN FC analyses(Cisler et al. 2012;Cisler et al. 2013), we would characterize FC with these seed regions using the following approach within each individual separately. First, we would extract the first principal component timecourses of 6 mm spheres centered separately on the three ROIs. Second, the seed region timecourse would be regressed onto the timecourse of every other voxel (i.e., whole-brain analyses) using an autoregressive model (AFNIs 3dREMLfit) and using an *r*-to-*z* transformation to improve normality. This would result in a separate whole-brain spatial map, indicating its degree of FC with the seed region, for each ROI and each participant.

Defining the effect of L-DOPA and dopamine gene score on striatal and mid-brain FC. Between-group GLMs would analyze functional connectivity (FC) using a 3 (group: placebo vs 100 mg L-DOPA vs 200 mg L-DOPA) x 2 (cue: CS+ vs CS-) x 6 (dopamine gene score: 0 [low endogenous dopamine] – 5 [high endogenous dopamine]) between-subjects ANOVA in a whole-brain, mass univariate, approach. Covariates of non-interest would be included if the "urn" balanced randomization procedure should fail to match groups on demographic and clinical severity variables. Cluster-level thresholding would be used to correct for multiple comparisons. This approach would identify clusters of voxels where FC with the SN/VTA, DC, or VS differed significantly as a function of L-DOPA, dopamine gene score, or the interaction. This analysis establishes the engagement of the intermediate mechanism in the proposed conceptual model hypothesized to mediate dopamine neurotransmission's pro-extinction effect.

Testing the effect of altered resting-state FC on fear extinction learning consolidation. Following identification of regions where FC with the DC, VS, and SN/VTA differ as a function of the L-DOPA x gene score interaction, we would then test whether individual differences in FC within these clusters predict subsequent consolidation of fear extinction learning. That is, we would test whether the hypothesized intermediate mechanism (acute dopamine neurotransmission and downstream dopaminergic neural networks) is related to the ultimate mechanism of interest (fear extinction learning). Consolidation of fear extinction learning from Day 1 would again be tested using Day 2 fear expression indices in Context A and Context B (i.e., fear extinction learning recall test) using multimodal assessments (neural circuit indices, psychophysiological, and self-report). GLMs would be used in which the outcome variable is regressed simultaneously onto the FC cluster, L-DOPA group, dopamine gene score, cue, and context. This would be repeated for the separate fear expression indices, with FDR controlling for alpha inflation due to multiple comparisons. These analyses would identify the clusters of voxels whose FC with the VS, DC, and SN/VTA predict enhanced recall on Day 2.

H. Dissemination of Data

All data will be deidentified. Publication of results will only include group level statistics: data will not be reported separately for any individual.

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