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Neural Correlates of Socially Rewarding Memories in Posttraumatic Stress Disorder

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Neural Correlates of Socially Rewarding

Memories in Posttraumatic Stress Disorder

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To my loved ones, including friends and pets: without your support through the most trying of times, I would not have been able to reach this milestone. Thank you to Catherine my senior cat for knowing exactly when to give me space and when to remind me it's ok to take a break to feed and love on you! You have always reminded me the importance of work life balance.

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ABSTRACT

KYLE P. BLIDY. Neural Correlates of Socially Rewarding Memories in Posttraumatic Stress Disorder (PTSD) (Under the direction of JANE JOSEPH).

Significance. Memory disturbances for emotional content are central to PTSD, yet most research focuses on trauma memories. Recent evidence suggests that enhancing access to positive memories could improve mood, affect regulation, self-esteem, and integration of trauma memories. However, the neurocognitive mechanisms underlying positive memory encoding in PTSD are poorly understood. No study has examined memory for positive social items in PTSD, which is important because PTSD entails social withdrawal and reduced accessibility to positive memory. Additionally, positive memories embedded in a social context have enhanced subjective value and strengthening their accessibility may confer greater benefits to wellbeing compared to non-social positive memories. **Approach.** Adults with PTSD (N=14) and trauma-resilient control individuals (TRC, N=18) completed a social reward task during functional magnetic resonance imaging. In this task, participants received evaluations according to whether unfamiliar peers "expected to like" the participant if they met in real life. Evaluations received were either favorable or neutral (i.e., no rating). Post-scanning, participants completed an episodic memory exercise wherein they indicated who had rated them favorably or did not rate them at all. Contrasts between successfully encoded social conditions were examined at the voxel-level with psychophysiological interaction using the bilateral amygdala (AMY) as seeds and hippocampi (HIP) as primary ROIs. Post-hoc general linear models (GLMs) were conducted to probe moderation by diagnosis and symptom severity. Recognition performance was similarly assessed using GLMs considering diagnosis, valence, diagnosis x valence, and sex as a covariate. **Findings.** No recognition performance differences emerged between PTSD and TRC groups, and AMY-HIP connectivity differences were limited to the neutral condition. Whereas functional uncoupling occurred during neutral memory encoding for TRCs, AMY-HIP co-activation was observed in PTSD. Symptom severity did not explain variability in AMY-HIP connectivity within the PTSD sample. **Conclusions.** Although positive memories may have distinct phenomenological characteristics in PTSD samples, quantitative indices of performance for rewarding social memories are similar between PTSD and TRC individuals. Notwithstanding, individuals with PTSD may inappropriately activate emotional memory networks in neutral contexts, suggesting an overgeneralization of emotional processing. Thus, this study provides evidence of dysfunctional emotional memory processing in non-trauma, neutral situations within PTSD samples.

CHAPTER ONE: INTRODUCTION

I. WHAT IS PTSD

Posttraumatic stress disorder (PTSD) is a common reaction following severe psychological trauma. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) classifies psychological trauma as "*exposure to actual or threatened death, serious injury, or sexual violence"* [1]. This exposure can occur though "*directly experiencing the event(s); Witnessing, in person, the event(s) as it occurred to others; Learning that the traumatic event(s) occurred to a close family member or close friend; or experiencing repeated or extreme exposure to aversive details of the traumatic event(s) (e.g., first responders collecting human remains; police officers repeatedly exposed to details of child abuse).*" Given this broad definition, epidemiological studies estimate that between 80-90% of the general population experience a traumatic event during their lifetime [2, 3]. This is a concerning statistic since trauma exposure is recognized as among the most prevalent and often preventable risk factors for mental and physical ill-health including, but not limited to, PTSD [4].

Within the framework of the DSM-5, PTSD is defined by symptoms occurring across four symptom clusters. Criterion B includes "*intrusions*," or the involuntary reliving of traumatic events and emotions; Criterion C includes "*avoidance*" behaviors, which may be either internal (thoughts or feelings), or external (people, places, or situations); Criterion D, titled "*negative alterations in cognition and mood*," encompasses symptoms similar to depression, such as anhedonia, inappropriate self-blame, and an inability to experience positive emotions like love and happiness; Finally, Criterion E, *"alterations in arousal and reactivity,"* refers to the sensitization of stressors (e.g., hyperarousal), aggression, and difficulty with concentration and sleep. In order to meet diagnostic criteria, these symptoms must occur for more than one month (Criterion F), cause marked impairment in social, occupational, and/or other areas of functioning (Criterion G), and

"*not [be] attributable to the physiological effects of a substance (e.g., medication or alcohol) or another medical condition*" (Criterion H) [1].

II. PTSD IS A PUBLIC HEALTH CONCERN

Estimates of PTSD lifetime prevalence vary widely due to differences in sampling methodology and population (e.g., civilian vs. military), with suggested estimates ranging from 8% to 20% [5, 6]. Globally, PTSD is probably underdiagnosed, yet even the most conservative estimates indicate that more than 310M people will face PTSD in their lifetime [7]. These staggering figures underscore the pervasive impact of trauma and PTSD.

The rate of disability from PTSD is also higher than that of most leading physical disorders [8]. PTSD confers significant impairments in all domains of quality of life defined by the World Health Organization (WHO) International Classification of Functioning, Disability and Health (ICF; [9]). Accordingly, PTSD is related to vulnerabilities of unemployment [10], homelessness [11], and incarceration secondary to behavioral sequelae of hostility and violence [12], as well as premature mortality and suicidality [13]. The ensuing economic burden of PTSD has been estimated to exceed $232B, equating to approximately $20,000 per patient annually [14]. For these reasons, the National Institutes of Health (NIH) and Veterans Affairs/Department of Defense (VA/DoD) have issued a call to action on advancing PTSD therapeutics. In 2018 alone, the NIH and VA/DoD spent over $136 million in 2018 for PTSD research and training [14]. In response to these initiatives, the present study sought to identify neural mechanisms that could serve as novel targets for PTSD intervention.

III. CURRENT STATE OF GOLD-STANDARD THERAPIES FOR PTSD

Nearly four decades ago, Foa and Kozak proposed the Emotional Processing Theory (EPT), which lends itself to the current framework of PTSD treatment [15]. EPT emphasizes that traumatic

events cause the formation of new associations between previously unrelated factors, such that these trauma-related or innocuous stimuli are then perceived as threatening. Activation of the fear network by trauma reminders causes threat-related information to enter consciousness (intrusions), followed by attempts to suppress such activation (avoidance). Given the necessity to curb the pathological fear structures that do not accurately represent reality, first-line interventions for PTSD are ones that involve revisiting distressing elements of the traumatic event and confronting maladaptive cognitions (e.g., helplessness) [16].

Prolonged Exposure (PE) [17], Cognitive Processing Therapy (CPT) [18], and Eye Movement Desensitization and Reprocessing (EMDR) [19] are first-line psychotherapies for PTSD endorsed by the American Psychological Association (APA) and VA/DoD guidelines [16, 20]. PE aims to re-activate the cognitive fear structure by gradually confronting trauma-related stimuli and providing corrective information about the trauma's consequences [21]. CPT uses Socratic dialogue and writing exercises to help patients integrate trauma into existing schemas. This involves extensive psychoeducation and addressing "stuck points," or problematic cognitions [18]. Finally, EMDR involves recalling traumatic memories while tracking movements with the eyes [19, 22]. It is based on the theory that negative beliefs and behaviors arise from dysfunctionally stored memories that overwhelm information processing systems. By taxing working memory, EMDR reduces the emotionality and vividness of the trauma memory, facilitating reduced sympathetic response and memory reconsolidation [23, 24].

PE, CPT, and EMDR are efficacious in mitigating PTSD symptoms as evidenced across numerous meta-analyses [25, 26], however they all have room for growth. First, a significant number of individuals prematurely discontinue (i.e., referred to as “dropout”; [27]). Dropout for trauma-focused treatments ranges between 28% and 68% [28, 29], and averages at 36% [30]. This means trauma-focused therapies have dropout rates *double* that of *non*-trauma-focused (e.g., *non*- gold-

standard) treatments (18.28%) (see meta-analyses by [30, 31]). Although one can speculate that dropout could be due to early recovery, research supports the opposite: only a minority of individuals dropout because they have remitted [32]. Instead, the majority of individuals who dropout are unchanged from baseline or have even deteriorated [33]. Critically, dropout rates peak just before the *exposure* element of therapy [34, 35], suggesting that the idea of trauma re-*exposure* reduces tolerability [31]—and efforts should focus on enhancing tolerability.

V. PTSD MAY BE CONCEPTUALIZED AS A DISORDER OF MEMORY DYSFUNCTION

Recent frameworks conceptualize PTSD as a disorder of memory [36-38]. Cardinal symptoms of PTSD include involuntary and intrusive memories of the trauma experience alongside paradoxical traumatic amnesia [39]. This means some individuals with PTSD report spontaneously—and vividly—reliving their trauma event as if it were happening "right now" [40]. Yet, they also struggle to *intentionally* retrieve a complete memory of the traumatic event. Instead, their recollection tends to be fragmented, poorly organized, lacking detail, and uncertain with respect to the temporal order of events [40]. The inability to remember details of the trauma may subsequently reinforce other core features of the disorder, such as negative beliefs about oneself being permanently damaged or excessive self-blame because something worse may have happened that cannot be remembered. Given all of this, some propose that persistent memory symptoms drive continuity of all other features of the posttraumatic stress syndrome [36, 41, 42].

Related, a recent clinical trial comparing various therapeutic approaches in over 700 Veterans determined that PTSD symptoms impinging on memory unanimously responded *least* to treatment [42]. The Intrusion symptom cluster remitted in 15.8% of patients. Additionally, *no* changes pre-post treatment across *any* modality were noted for specific mnemonic features of feeling or acting as if the traumatic event(s) were recurring (i.e., flashbacks), physical reactions to

trauma reminders, and inability to recall an important aspect of the trauma. Levi et al. [42] concludes by asserting therapeutic advancements will require "*augmentation of extant treatments or developing new treatments that target the [memory] symptoms of PTSD that do not respond well to extant treatments*."

Complementing clinical findings, numerous laboratory studies reveal individuals with PTSD experience persistent memory alterations. Compared to healthy individuals, those with PTSD often exhibit enhanced memory for negative or trauma-related cues. This enhanced recall for negative stimuli in PTSD has been observed in studies using tasks like free recall of words [43-46] and pictures [47], word-pair tasks [48], and word completion tasks [49]. Additionally, PTSD symptom severity may positively correlate with the recall accuracy of negative words [50] and recognition accuracy of fearful faces [51].

While not all studies show a unique negativity memory bias in PTSD (e.g., [52-55]), many of those with null findings still report a trend toward false recognition of negative words [53, 54] and images [55, 56]. Overall, PTSD involves a bias toward negative information, which may re-activate the fear network [15] and reinforce core symptoms, complicating recovery.

VI. IS PTSD ALSO A DISORDER OF POSITIVE MEMORY DYSFUNCTION?

If PTSD is perpetuated by negative memories, this should also imply deficits related to memory for positive events. This rationale is not new; In fact, most trauma theories emphasize a broad role of memory in individuals with PTSD symptoms [15, 40, 57]. Yet, current trauma research and clinical work only consider half the picture, as they primarily focus on traumatic memories which are negative [58, 59].

The few laboratory studies that have considered positive memories in PTSD have yielded mixed results. Some studies found no differences in recognition memory for positive pictorial scenes between PTSD and healthy samples [60, 61], while others reported only small effect sizes for PTSD-related deficits in positive memory using free- and cued recall of word pairs [46, 49, 62]. Notably, these laboratory recall/recognition studies do not fully align with self-report evidence, which suggests that individuals with PTSD recollect substantially fewer pleasant life events [63]. They also do not replicate the findings of several narrative studies where patients recounted fewer detailed memories of personally relevant autobiographical events (e.g., [64-66]). The discrepant results across PTSD studies could stem from methodological variations; some studies used binary metamemory judgments of positive memory (e.g., 'Is this word familiar?'), while others required responses to cues that prompted open-ended recollections. Additionally, the tasks in prior studies varied with respect to their personal significance, such as remembering items from a database versus an event from one's own past. As a result, it remains unclear whether PTSD specifically alters personally relevant memories or if its impact on positive memory is more nuanced and limited to the phenomenological qualities of autobiographical memory, such as vividness and detail.

Insights gained about positive memory processing in PTSD could guide intervention targets. Recent work has already demonstrated that complementing extant therapies with tools to facilitate higher availability of positive memories could augment client engagement, increase readiness to start trauma-focused interventions, reduce fear in discussing traumatic memories, and decrease dropout rates [38, 67-71]. Accordingly, the extent of specific positive memory deficit is inversely correlated with PTSD symptom severity and self-blame [67]. To illustrate this, one study of trauma-exposed individuals showed that prompting recall of specific positive memories significantly reduced PTSD symptom severity, post-trauma cognitions, and negative affect for at

least one week [68]. Favorable outcomes secondary to positive memory induction are likely due to affect regulation via shifting attentional bias away from negative content [72] and increasing positive interpretations of events [73]. Positive memories may serve as personal reference points from which the interpretation of other experiences and personal identity are formed.

Bolstering accessibility to positive memory may be clinically challenging because restricted access to positive memories contributes to both the etiology and maintenance of PTSD (i.e., transdiagnostic construct) [74, 75]. Indeed, pre-trauma risk factors of PTSD include genetics (e.g., PRKCA polymorphism) that can influence encoding of emotional memories [76]. Similarly (as mentioned), individuals with PTSD report difficulties accessing specific positive (e.g., self-relevant) memories, and instead retrieve autobiographical information in an abstract and over-generalized manner (e.g., "the day we had a picnic in last summer's heat wave vs. enjoying picnics on summer days." [77]). This impedance in moving from categorical (i.e., a whole class of events) to specific memory (i.e., an event at a certain time/place) retrieval has been linked to diminished executive resources, even after controlling for depression [74]. These are important experimental findings because preoccupation with intrusive memories of trauma, which is characteristic of PTSD, may bias attention toward negative information and deplete cognitive resources, together making it even more difficult for a traumatized person to use memory in a specific adaptive fashion, and exacerbating the deficit in access to positive memory. For these reasons, Contractor et al. [38] recognize an impetus for translational research on positive memories in PTSD and trauma-exposed samples—especially in the context of access and retrieval. They argue that "*such information could guide intervention targets to enhance the benefits of processing positive memories*."

VII. THE VALUE OF POSITIVE MEMORIES CAN BE ENHANCED IN THE SOCIAL CONTEXT

Positive memory retrieval generates pleasant feelings that can counteract negative affective states and improve mood [72]. This is analogous to a snowball effect because positive memories tend to be long lasting and richly associative, thereby cueing the recollection of others [78]. Many nostalgic experiences are ones embedded in a social context (e.g., celebrating a birthday with others vs. receiving good grades) [79]; thus, retrieving memories in a social context may confer *additional* protective benefits during stress. A recent study by Speer et al. [80] compared reward system activation in healthy individuals who underwent stress induction, followed by recounting social versus nonsocial episodic memories during fMRI scanning. The investigation found (1) greater activation of the left caudate (associated with reward) during retrieval of social compared to nonsocial events; and (2) steeper reductions in cortisol level after stress induction following recounting of social versus nonsocial events.

The ability to draw upon self-preserving social memory could be limited in patients with PTSD because a direct relationship between remembering social interactions and actively participating in social behavior has been noted in healthy individuals [81]. Indeed, a meta-analysis of 23 retrospective studies concluded that the lack of social support (i.e., isolation) is among the strongest predictors of PTSD in the aftermath of trauma—and is associated with progressive symptom exacerbation [82, 83]. A 14-year longitudinal study among Vietnam Veterans also found that psychosocial impairment was closely associated with persistent PTSD almost 30 years *post*-deployment [84]. Lack of social support appears to play a key role in the etiology and maintenance of PTSD and positive social support is one of the best predictors of recovery in PTSD [82]. Despite this, neural mechanisms underlying the rewarding nature of social interactions and memories are poorly understood. Elucidating the neural underpinnings of positive, socially rewarding memory

encoding in PTSD may allow for therapeutic advances that could boost or improve memory function for recollection of socially rewarding stimuli and promote recovery.

VIII. EMOTIONAL MEMORY AND SOCIAL BEHAVIOR ARE SUBSERVED BY OVERLAPPING BRAIN REGIONS THAT ARE DYSREGULATED IN PTSD

PTSD is associated with a selective enhancement in memory for negative valence stimuli [43, 46] coupled with a deterioration in the retrieval of positive and neutral stimuli [67]. This is behaviorally logical, as patients with PTSD, much like individuals with depression, preferentially remember mood-congruent negative information [85, 86]. In contrast, healthy adults possess self-regulatory mechanisms that lead to better memory performance (including richness of detail) for positive versus negative material [87], followed only then by negative versus neutral material [88, 89].

From a neuroscience perspective, the enhancement of emotional memories is likely due to their arousing nature which captures attentional resources and co-recruits the amygdala (AMY) and hippocampus (HIP) (see meta-analysis by [90]). The AMY is reliably activated during presentation of emotional stimuli [91], including among patients with PTSD [51]. Such affective salience influences the formation of a HIP-dependent cognitive memory system, resulting in a long-term memory that is associated with greater retention [92]. In healthy individuals, synergistic activation of the AMY and HIP occurs in both appetitive [93] and fear-provoking conditions [94], contributing to the robust emotional > neutral memory bias. However, what is unknown is how the AMY-HIP is affected in individuals with PTSD who tend to have a dissociation in emotional memory function, such that *only* negative memories are prioritized (negative/fear > neutral ≥ positive/appetitive).

Memory in PTSD may be disrupted because the disorder alters the HIP, ventromedial prefrontal cortex (vmPFC), and AMY [95]. The HIP, known to subserve declarative (emotionally neutral) memory [96], is dense in glucocorticoid receptors, making it a primary target of stress-induced

neurotoxicity [97]. The HIP tends to undergo dendritic atrophy, leading to reduced size among adults with PTSD [98]—and declarative memory decrements are correlated with the extent of reduction in HIP volume [99]. AMY volume changes are inconsistently found in the literature [100]; however, the prioritization of negative-valence memories observed in PTSD may be a consequence of AMY hyperactivity toward negative stimuli, according to a review of neuroimaging studies in patients with PTSD relative to healthy controls [101]. Lending some support to preferential recruitment of the AMY during negative information processing in humans with PTSD, numerous studies find the basolateral nuclei (BLA) to be more strongly activated in patients relative to trauma resilient control (TRC) individuals when viewing threat stimuli (e.g., [102, 103]). Additionally, one investigation found the BLA to be more activated during successful encoding of negative scenes in PTSD relative to TRC individuals [104]. Lastly, other studies examining functional connectivity between the AMY and HIP during encoding of negative versus neutral pictures showed that the PTSD group had "exaggerated" coupling compared to controls [105]. This has led some to speculate that AMY-HIP connectivity underlies (negative) intrusive memory symptoms in PTSD [106].

The impact PTSD has on AMY activation and AMY-HIP functional connectivity, however, remains poorly characterized with respect to positive stimuli. One of the few published studies is constrained by an extremely low sample size (i.e., N = 10 within PTSD and control groups) [107]. Another study involved passive viewing of schematic stimuli (i.e., 240 grey-scale faces across 30 blocks) to elicit positive emotions [108]. This approach lacks ecological validity [109] as well as risks neural habituation, which may obscure differences in AMY and/or HIP activity due to the task's repetitive nature [110]. Finally, other studies on positive memory encoding in PTSD used stimuli that were significantly less arousing than negative stimuli [61, 105, 111], complicating the

interpretation of neural patterns compared by emotional valence. Overall, it remains largely unknown how individuals with PTSD process and encode positive social stimuli.

Aside from their established role in emotional (especially negative) memory, animal research has demonstrated that the AMY and HIP are also involved in social behavior. For example, in macaques, inhibiting the BLA using muscimol (a GABA receptor agonist) *increases* social interactions like partner grooming [112]. Extending this framework, research in mice shows that when the BLA-ventral HIP circuit is optogenetically *inhibited*, mice explore more socially. However, *activating* this circuit causes mice to *avoid* new conspecifics and engage in stress-related behaviors like self-grooming [113]. These findings highlight that the AMY and HIP are mechanistically (and causally) related to both social behavior and stress—potentially supporting the human literature that social support (and associated memories) can counteract stress.

IX. RESEARCH GAP, AIMS, AND HYPOTHESES

The proposed study aims to bridge two understudied constructs–positive memory and social reward—each contributing to the etiology and maintenance of PTSD. Although a wealth of knowledge exists on memory alterations in PTSD, several research gaps to date have precluded therapeutic advances. Specifically, the associations between traumatic events, PTSD symptoms, and positive memories are not well characterized. The few studies that have examined positive memory in laboratory settings have either not detected differences between PTSD and healthy samples in recognition performance for pictorial scenes [60, 61, 104] or detected meager effect sizes for PTSD-related memory deficits using recall of word stimuli [46, 49]. These paradigms might not robustly detect memory impairments in PTSD because they lack the ingredients comprising positive memory used in everyday life (i.e., autobiographical memory). Therefore, to capture

essential elements of memory that are impaired in PTSD, a more ecologically valid task using personally-relevant socially rewarding stimuli is needed.

Neural correlates of memory encoding in PTSD have been examined before (e.g., review [114]), but past studies did not always compare against a control group [51], only considered negative versus neutral stimuli [52, 53, 105, 115, 116] or considered traumatic versus "nontraumatic" stimuli [117]. Patel et al. [104] was a noteworthy exception because they collected data on positive memory encoding among PTSD and TRC samples; however, they were also among the studies that used database stimuli of questionable ecological relevance. Additionally, their analysis was restricted to activation across sub-regions of the AMY (BLA vs centromedial nuclei), so, Patel et al. [104] did not consider functional connectivity with the HIP, a key contributor to successful encoding of emotional memory [118-120]. AMY-HIP connectivity during encoding of positive memories remains unknown in PTSD.

Characterizing how the brain creates (encodes) memory for positive events—especially ones that are socially rewarding—could be beneficial for augmenting PTSD treatments. For instance, the ability to remember positive information has been shown to promote effective coping strategies [121], which could reduce therapy avoidance [122]. Additionally, positive memories may promote retention/readiness to initiate trauma-focused interventions because the positive affect states they support can counteract negative affect states elicited by distressing re-exposure elements of therapy [121]. Alternatively, because recollection of positive memories reduces stress [80] and inspires pro-social behavior [81], boosting positive memory encoding could be a meaningful complement to psychosocial therapies aimed at repairing interpersonal relationships.

With this, the primary objectives of the current study are two-fold, (i) to examine differences in memory recognition of socially rewarding stimuli between individuals with PTSD and TRC

individuals; (ii) to use functional magnetic resonance imaging (fMRI) to characterize functional connectivity between the AMY and HIP during memory encoding of positive, socially rewarding stimuli. Hypothesis 1 is that individuals with PTSD will recognize fewer face-feedback pairings corresponding to positive, socially rewarding, memory compared to TRC individuals. Hypothesis 2a is that AMY-HIP connectivity will be weaker during successful encoding of socially rewarding events among individuals with PTSD versus TRC individuals. Hypothesis 2b is that AMY-HIP connectivity strength during successful encoding will be negatively correlated with PTSD symptom severity.

CHAPTER TWO: METHODS

I. PARTICIPANTS

Recruitment occurred via internet advertisements (e.g., Craigslist, Facebook), clinician and community referrals, and via IRB-approved flyers in the community. Potential participants were contacted by phone and invited to complete a prescreener to determine preliminary eligibility. Individuals included in the study were fluent in English, ambidextrous or predominately right-handed, and 22-55 years of age. This age range was selected to enhance recruitment and generalizability of the findings while constraining factors associated with age that may confound the results. Children, adolescents, and adults under the age of 22 were excluded to reduce variability in MRI data acquired from individuals who do not yet have fully matured brains. Adults older than 55 were not included to ensure cognitive and biological developmental changes related to age do not confound study findings. Similar age ranges covering nearly 30 years of adulthood have been used in recent memory studies of PTSD and TRC individuals (e.g., [41]).

Inclusion criteria. The PTSD group (N=14) met criteria for PTSD on the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) [123] with a severity score of 25 or higher. The TRC group (N=18)

endorsed a DSM-5 criterion A traumatic event, as per the Life Events Checklist for DSM-5 (LEC-5) [124] and CAPS-5 but did not meet full PTSD criteria on CAPS-5, had a severity score of ≤12, and had no lifetime PTSD diagnosis.

Exclusion criteria. Participants in both groups were excluded if they had: (a) a positive pregnancy test, (b) current or history of any major medical, neurological, or psychiatric condition (i.e., bipolar, psychotic disorders) that could compromise safety or the data (assessed by self-report and Quick SCID), (c) an implant or device contraindicated for the neuroimaging procedures or a metallic foreign body (e.g., pacemaker, ferromagnetic aneurysm clip), (d) current suicidal ideation and intent, (e) current use of psychoactive medications that affect cerebral blood flow (e.g., angiotensin-converting-enzyme inhibitors, beta blockers, antihistamines, calcium channel blockers), (f) current use of a psychotropic medication (e.g., selective serotonin reuptake inhibitors) for less than four weeks, (g) current participation in a randomized controlled trial for PTSD, (h) concurrent or lifetime substance use disorders, except nicotine and cannabis. Cigarette and marijuana use were *not* exclusionary due to their very high prevalence in PTSD samples (Lake, Kerr et al., 2019). However, any participant who endorsed being a daily user of tobacco or cannabis and/or met criteria for a severe tobacco use disorder or severe cannabis use disorder was excluded.

II. MEASURES

Participants who met initial eligibility via the prescreen were invited to schedule a baseline study visit. This appointment took place remotely via a secure, MUSC-approved, videoconferencing platform. At the start of the appointment, participants were given a full description of the study procedures and asked to read and sign an IRB-approved informed e-consent form. After the

consent form was signed and dated by both the participant and researcher, it was shared digitally with the participant.

During the remainder of the baseline visit, participants completed a battery of standardized self-report and interview measures (Table 1). The LEC-5 [124] was used to assess trauma exposure; The CAPS-5 was used to assess PTSD and determined participant eligibility and group (PTSD vs. TRC) designation. Participants were evaluated for safety to undergo the neuroimaging scan using MUSC's metal screener. The social reward task and corresponding neuroimaging scheduling procedure are described in detail below.

III. PROCEDURES

Social Reward Task. The current study used a social reward paradigm analogous to that of prior investigations [125-127] (Timeline in Figure 1). During the "faces rating task" (occurring at baseline), participants were presented images of 60 unfamiliar racially and ethnically diverse peers acquired from the Chicago Face Database [128] (Table 2). Face stimuli were selected based on normative ratings to ensure (i) an equal distribution by sex, (ii) an equal age range (25-50 years) and distribution of perceived age within each sex (e.g., M = 34.45 years, SD = 5.7 in male stimuli; M = 34.95 years, SD = 5.6 in female stimuli), (iii) low ratings of perceived negative and positive valence, and (iv) matched attractiveness by sex. Participants were asked to rate how much they would anticipate liking each individual if they were to meet "in real life," using a 1-9 scale (1 = "not at all"; 9 = "very much"). Deception was used insofar as participants believed that a photo taken of them during the study procedures would receive reciprocal evaluations from these peers. In reality, the photo taken of each participant was discarded.

Table 1

TABLE 1. Assessment Instruments

Instrument Name	Purpose/Domain	Pre	BSL	Neuro
Prescreener	Pre-screen participants for preliminary eligibility	✓		
Informed Consent	Obtain informed consent		✓	
Demographics Form	Characterize sample		✓	
History of Head Injuries	Study eligibility		✓	
Concomitant Medications Form	Monitor medications, study eligibility		✓	
MRI Screening Form	Study eligibility, safety		✓	✓
Pregnancy Test (for people of childbearing potential only)	Study eligibility		✓*	✓
Quick Structured Clinical Interview for DSM-5 (Quick SCID)	Assess DSM-5 psychiatric disorders (major depressive disorder, substance use disorders, bipolar		✓	
Fagerstrom Nicotine Dependence Test	Assess nicotine dependence		✓	
Life Events Checklist for DSM-5	Assess trauma exposure		✓	
Clinician Administered PTSD Scale for DSM-5 (CAPS-5)	Assess PTSD & severity (clinician rated)		✓	
PTSD Checklist for DSM-5 (PCL-5)	Assess PTSD symptom severity (self-report)		✓	
Philadelphia Adverse Childhood Events (ACEs) Scale	Assess childhood trauma exposure		✓	
Interpersonal Support Evaluation List (ISEL)	Assess social support		✓	
Dyadic Adjustment Scale – short form (DAS) (for persons in an intimate relationship only)	Assess intimate relationship functioning		✓	
Revised Conflict Tactics Scale (CTS) (for persons in an intimate relationship only)	Assess intimate partner violence		✓	
Cognitive Emotion Regulation Questionnaire (CERQ-Short)	Assess emotion regulation strategies		✓	
Insomnia Severity Index (ISI)	Assess sleep functioning		✓	
Patient Health Questionnaire (PHQ-9 and PHQ-15)	Assess depressive & physical symptoms		✓	
Faces Rating Task	Evaluate age matched peers based on first impressions		✓	
Social Reward Task	Identify neural correlates of social reward		✓	✓

Note. Pre = prescreening; BSL = Baseline visit; Neuro = Neuroimaging visit. *Only for visits conducted in-person.

Clinical instrument selection. The CAPS-5 has excellent psychometric properties, including good interrater reliability (κ = .78 to 1.00) and test-retest reliability (κ = .83) (Weathers et al., 2018). The PTSD Checklist for DSM-5 (PCL-5) (Weathers et al., 2013) was used to correlate a clinically meaningful measure to fMRI findings in Aim 2b. The PCL-5 is a 20-item self-report measure of PTSD symptoms experienced in the last week and has sound psychometric properties (e.g., internal consistency [α =.96], test-retest reliability [r = .84] (Bovin et al., 2016), and convergent [r's = .74 to .85] and discriminant [r's = .31 to .60] validity) (Blevins et al., 2015).

Figure 1

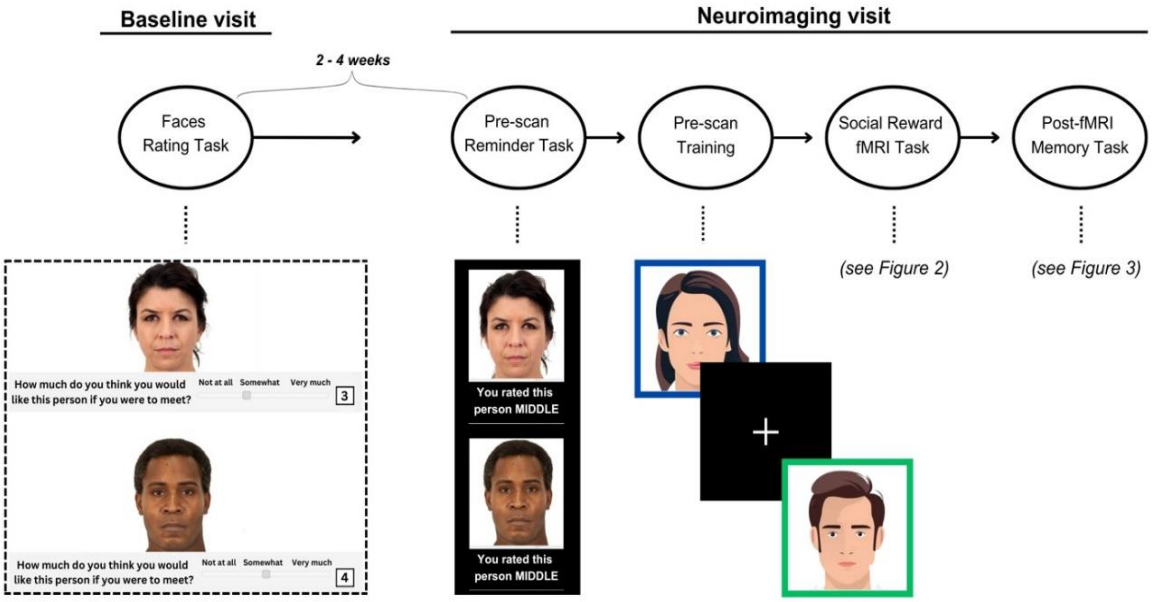


Figure 1. Timeline of the social reward task. At baseline, participants provide likeability ratings to unfamiliar (fictitious) peers. Following this, participants have their own photo taken, under the pretense that they will later receive likeability evaluations from these peers. The neuroimaging session, conducted at least two weeks later, begins by reminding participants of their baseline categorical ratings previously given to peers (high, low, or neutral/middle). Participants then complete an exercise to learn novel task instructions; information conveyed about likeability evaluations received from peers would be conveyed with color. Positive feedback from peers takes the form of that peer's photo enclosed in a green border. In contrast, a blue border signals that the peer did not provide feedback (neutral condition). During the fMRI portion of the task, participants receive this social feedback, aimed at capturing the neural processes involved in social reward. The final component completed post-fMRI, interrogates memory recognition by asking participants to determine which peers rated them favorably or not at all.

Table 2

Chicago Face Database Stimuli Selection (Organized by Sex)

Stimulus ID	Age	Negative Valence	Positive Valence	Attractive
White Male (N = 15)				
WM-214	25.12	1.75	3.40	3.12
WM-207	26.58	1.60	3.09	4.13
WM-257	30.04	1.70	2.52	3.74
WM-254	30.31	1.65	2.54	3.15
WM-023	37.59	1.93	3.39	2.87
WM-225	36.82	1.74	2.68	3.04
WM-248	41.69	2.18	2.31	2.85
WM-249	43.19	2.91	1.33	2.41
WM-211	27.79	1.66	1.97	3.46
WM-213	26.36	1.82	3.83	3.71
WM-252	32.78	2.00	2.70	3.11
WM-258	37.85	1.66	3.07	2.15
WM-248	41.69	2.18	2.31	2.85
WM-204	35.13	1.82	2.10	3.20
WM-029	28.59	1.88	2.67	4.59
mean (SD)	33.43 (5.92)	1.90	2.66	3.22
Black Male (N = 6)				
BM-214	27.37	1.87	3.15	3.52
BM-250	34.93	1.48	2.69	3.52
BM-236	38.36	1.88	3.93	3.61
BM-228	38.77	1.81	3.04	4.00
BM-245	43.74	2.77	2.26	3.09
BM-200	26.48	1.55	2.93	3.22
mean (SD)	34.94 (6.23)	1.89	3.00	3.49
Asian Male (N = 3)				
AM-218	33.59	1.39	2.86	3.21
AM-235	35.16	2.03	2.08	2.36
AM-227	41.42	1.71	1.88	2.38
mean (SD)	36.73 (3.38)	1.71	2.28	2.65
Multiracial Male (N = 2)				
MM-311	34.04	2.00	2.72	2.38
MM-303	42.04	2.39	2.23	2.45
mean (SD)	38.04 (4.00)	2.20	2.48	2.41
Hispanic Male (N = 3)				
LM-224	26.55	1.46	3.55	5.07
LM-227	32.28	1.69	2.55	3.07
LM-204	40.07	2.43	2.93	2.79
mean (SD)	32.97 (5.54)	1.86	3.01	3.64
Indian Male (N = 1)				
IM-709-103	37.21	2.25	2.89	2.74
mean (SD)	37.21 (0)	2.25	2.89	2.74

Stimulus ID	Age	Negative Valence	Positive Valence	Attractive
White Female (N = 15)				
WF-236	26.38	1.73	3.23	4.58
WF-013	26.42	1.67	3.60	3.57
WF-241	32.68	2.18	1.88	2.88
WF-023	32.74	2.16	3.05	2.74
WF-215	30.64	2.06	2.80	3.28
WF-250	36.80	1.70	1.84	1.72
WF-228	36.23	1.88	3.36	3.69
WF-246	42.82	2.12	1.68	3.54
WF-240	44.76	2.37	1.52	2.21
WF-214	28.34	1.92	2.38	3.21
WF-226	32.24	1.85	1.90	2.71
WF-222	38.80	2.10	2.83	2.53
WF-221	42.32	2.51	1.64	2.41
WF-245	35.71	2.34	2.11	3.43
WF-209	27.79	1.67	3.69	4.66
mean (SD)	34.31 (5.80)	2.02	2.50	3.14
Black Female (N = 6)				
BF-221	27.04	1.30	4.36	4.64
BF-204	31.50	1.55	3.33	4.00
BF-010	29.20	1.96	3.44	2.72
BF-220	33.34	1.43	2.50	2.27
BF-251	38.07	1.50	4.19	4.19
BF-238	45.68	2.06	2.72	3.28
mean (SD)	34.14 (6.21)	1.63	3.42	3.52
Asian Female (N = 3)				
AF-248	34.17	1.47	3.34	4.14
AF-238	37.56	2.15	2.00	2.89
AF-213	40.18	1.96	2.61	3.00
mean (SD)	37.30 (2.46)	1.86	2.65	3.34
Multiracial Female (N = 2)				
MF-355	35.33	1.90	3.50	4.38
MF-353	40.49	2.23	3.07	3.36
mean (SD)	37.91 (2.58)	2.07	3.28	3.87
Hispanic Female (N = 3)				
LF-249	28.52	1.53	3.86	5.24
LF-246	30.89	2.00	2.96	3.27
LF-238	42.33	1.79	2.90	3.03
mean (SD)	33.91 (6.03)	1.77	3.24	3.85
Indian Female (N = 1)				
IF618-212	39.76	2.59	3.16	3.87
mean (SD)	39.76 (0)	2.59	3.16	3.87

Upon completion of the faces rating task and other baseline procedures (i.e., self-report surveys), the neuroimaging (fMRI) visit was scheduled. To bolster study deception, a minimum of two weeks was given between baseline and fMRI visits so experimenters could "recontact" the fictitious peers for their ratings of the participant. However, to ensure reliability of clinical measures retrieved at baseline, all neuroimaging appointments were conducted within four weeks of baseline. Participants were instructed to abstain from nicotine, alcohol, and other substances (not including prescribed medications) for at least 24 hrs prior to the neuroimaging visit.

Stimuli customization. Personalized stimulus sets were developed for each participant based on their ratings of face stimuli at the baseline study visit. Of the 60 faces evaluated by the participant at baseline, only 32 face stimuli were selected for use during the neuroimaging visit. These 32 derived from one of three categories for each participant: *most*-liked stimuli (4 highest-rated male faces and 4 highest rated female faces), *least*-liked stimuli (4 lowest-rated male faces and 4 lowest-rated female faces), and *neutral* stimuli (8 male and 8 female faces not falling into either of the previous categories).

Neuroimaging visit. Upon arrival to the neuroimaging appointment, participants of child-bearing potential provided a urine sample to ensure the absence of pregnancy. Afterwards, and immediately prior to the fMRI scan, participants completed a "pre-scan reminder task." The pre-scan reminder task prompted participants to passively view the 32 selected photos of peers alongside corresponding category evaluations they provided for each (i.e., most-liked, least-liked, neutral). Specifically, each peer was presented on a black background and with large text (Arial size 30) underneath indicating "you rated this person" highest/lowest/middle, as applicable (Figure 1). Participants were instructed to remember each face and their own categorical rating of each to maximize personal relevance upon receipt of the social feedback. Each face was shown once for seven seconds and presented in block order (high, low, middle) across three blocks using

E-prime software (V.2; Psychology Software Tools) running on a Windows computer. The Inter-stimulus interval (ISI) lasted 3 seconds and the inter-block interval (IBI) was 8 seconds in duration.

Next, Participants were acclimated to the subsequent task prior to entering the scanner. This training involved four steps. First, Individuals were reminded that their photograph was taken at baseline and circulated with study participants (i.e., the fictitious peers) so they too could receive likeability evaluations. Second, participants were shown the two possible feedback options they would view during scanning: favorable- or neutral- feedback. Colors, rather than text, represented feedback conditions. Text was avoided to minimize gaze away from social (face) stimuli. A green border surrounding a peer's image indicated "*this person expected to like you and rated you highly*," while a blue border surrounding a peer's image indicated "*this person did not rate you.*" To enhance the element of deception, participants were told that a blue border (i.e., absence of feedback) could mean that peer was unavailable for contact or that peer ran out of time when evaluating their given list of subjects. Novel cartoon stimuli with neutral expressions were used in the practice exercise as a surrogate for peer faces.

The final pre-scan training steps involved more interactive instructions. In step 3, participants were told that during the coming fMRI task, they would see some repetitious stimuli, but that the evaluations provided (i.e., favorable, neutral) would be consistent. Regardless of repeats, they were to (1) press a button each time they saw a face on the screen (i.e., to ensure task engagement); (2) think about their own evaluations given to each peer when learning how that person rated them back; and (3) remember whether each peer had rated them favorably or not at all because they would be completing a post-fMRI memory exercise. The latter instruction represents a modification of the paradigm used in prior studies (37-39), done to promote attention and subsequent accuracy in the post-fMRI recognition task. Finally, the pre-scan training

concluded by confirming the participant understood the feedback conditions. All instructions were repeated after the participant was loaded onto the bed of the scanner.

Social Reward Task (fMRI). The fMRI task used a hybrid block/event-related design (Figure 2). The participant's most-liked, least-liked, and middle-liked stimuli gave rise to 3 types of blocks used in the task: *Mutual* liking blocks included stimuli with reciprocal favorable (i.e., rewarding) evaluations between the participant and fictitious peer; *Received* liking blocks also included stimuli with favorable evaluations, but from peers that the participant rated lowest/most *un*favorably; *Ambiguous* liking blocks included stimuli that the participant rated neutrally (i.e., middle), but that had no peer feedback at all. Four of the eight blocks were primarily composed of Ambiguous feedback faces; The remaining four blocks were predominantly composed of positive feedback faces: two representing Mutual liking- and two representing Received liking conditions. Both Mutual- and Received- liking blocks corresponded to stimuli with green borders, and the Ambiguous blocks contained face stimuli surrounded by blue borders. Peers who had ostensibly rated the participant *un*favorably were not shown at all because social rejection is not related to the aims of the current study.

Each of the 32 customized facial stimuli was shown two or three times across eight total blocks in a single run of the fMRI task (total time 9min 27s). Blocks were pseudorandomly ordered, with the order fixed for all subjects (Received 1, Ambiguous 1, Ambiguous 2, Mutual 1, Received 2, Ambiguous 3, Mutual 2, Ambiguous 4). To ensure that the same ambiguous condition faces did not repeat across consecutive blocks and have the potential to bias memory (i.e., Ambiguous block 2 following Ambiguous block 1), the 16 total ambiguous category stimuli were split, such that Ambiguous blocks 1 and 3 had the same stimulus set and Ambiguous blocks 2 and 4 had the same stimulus set. Additionally, balance and distribution of peer gender was ensured in all task blocks.

To further minimize predictability and habituation to the valence of stimuli in a particular block, each 10-item block included two non-condition stimuli. Specifically, two face stimuli from peers providing Ambiguous feedback were intermixed in Mutual- and Received liking blocks; and two positive feedback stimuli (one of each type, Mutual- and Received liking) were intermixed in each of the Ambiguous liking blocks. Placement of non-condition stimuli within each block was fixed across subjects.

Each face stimulus was shown for 3 seconds and interspersed with null events (a fixation screen) lasting 1.25, 2.5, 3.75, 5, or 6.25 seconds to allow for jittering the interstimulus interval (ISI) (Figure 2). Each ISI denomination occurred twice per block in a randomized fashion, with each block lasting 67.5 seconds. The interblock interval (IBI) was 8 seconds and contained a fixation screen. A five-button response pad was placed in subjects' right hand so that they could indicate viewing each face. Individuals were permitted to press using any finger they felt was most comfortable.

Figure 2

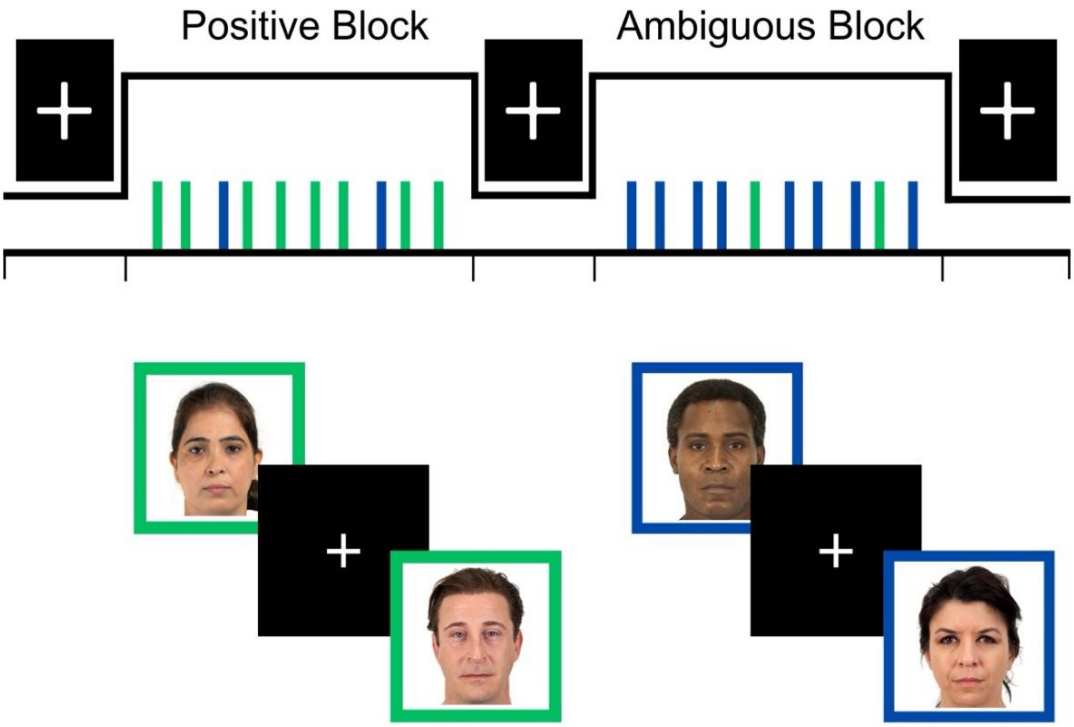


Figure 2. The fMRI component of the social reward task. Face stimuli were presented across eight blocks arranged in a hybrid block/event-related design. There were three task conditions: Mutual liking (reciprocal positive evaluations between participant and peer), Received liking (positive peer evaluations from those rated least favorably by the participant), and Ambiguous liking (neutrally rated peers with no feedback). Mutual and Received liking stimuli were framed in green borders, since they both conveyed positive feedback more generally, and Ambiguous stimuli were framed in blue borders. Each block contained ten stimuli, intermixed with two non-condition stimuli to minimize predictability. Face stimuli were presented for 3 seconds, followed by jittered interstimulus intervals (1.25-6.25 seconds). Total fMRI task duration was 9 minutes and 27 seconds.

Memory Task. After neuroimaging, participants immediately underwent a "post-fMRI memory task" (Figure 3). During this post-fMRI memory task, participants were shown the same 32 face stimuli in a random order using E-prime software running on a Windows computer. Each face was presented with two sequential questions: (1) "*Did this person rate you favorably?*" and (2) "*How did you feel when learning how this person rated you?*" Question 1 used a six-point scale to rate

confidence in memory: 1-3 corresponded to “did not rate me” and 4-6 corresponded to “rated me favorably,” with anchors for “maybe,” “probably,” or “definitely.” To aid in recognition, the continuum scale was color-coded in blue and green, (i.e., green corresponding to “favorable” answer choices 4,5,6). Question 2 permitted responses using a 1-9 Likert scale, with numeric values denoting varying levels of subjective feeling toward a particular peer. Participants were informed that "a higher number means a more positive feeling;” 9 indicated positive subjective feelings, 1 represented unpleasant feelings, and any value between 1 and 9 represented a subjective feeling neither completely positive nor negative about a particular peer. In lieu of text-based anchors, emoticons were placed at positions approximately 1, 5, and 9 along the scale, corresponding to negative, neutral, and positive emotions, respectively.

After the post-fMRI task, participants were debriefed about the deception: their pictures were neither seen by anyone outside the study team nor rated for likeability. To mitigate the chance that participants felt intellectually inadequate due to being deceived by study manipulations, they were informed that 90-95% of participants in comparable studies were similarly deceived [125-127]. To confirm understanding, participants repeated the task objectives. They then filled out forms on (1) continued consent for data use and (2) their belief in the deception and suggestions for improvement. Participants received $100 for their participation.

Figure 3

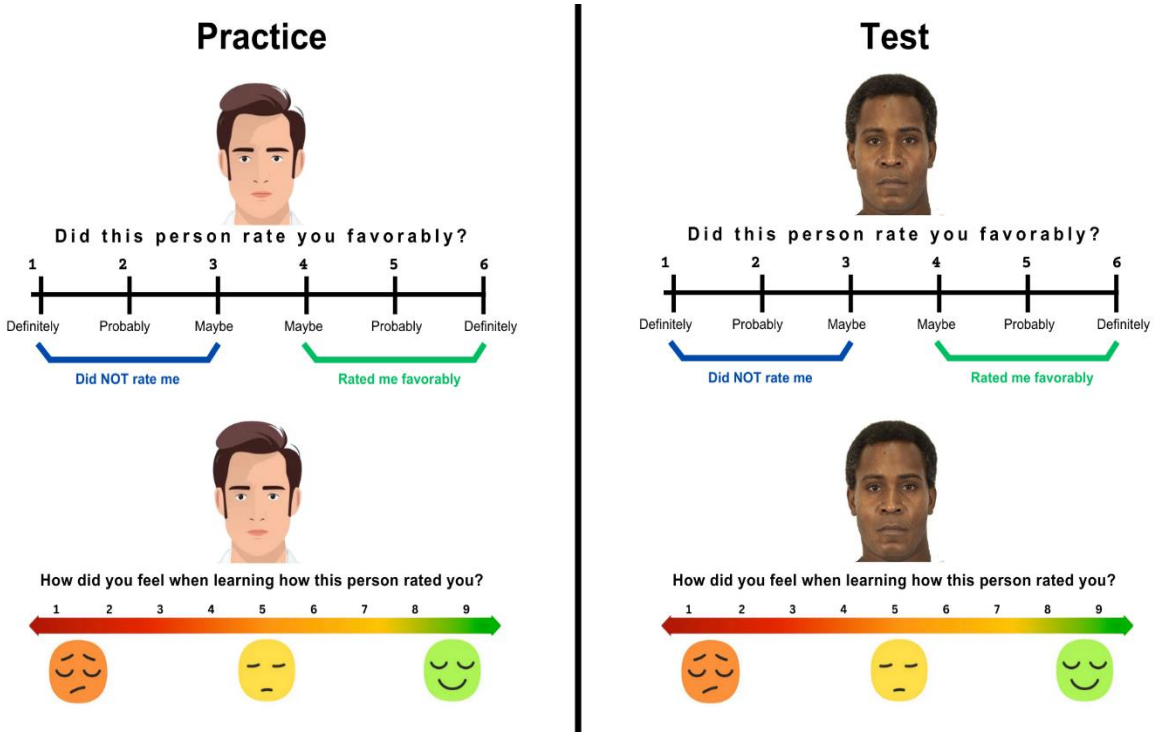


Figure 3. Post-fMRI Memory Task. Immediately after neuroimaging, participants completed a memory task in which they viewed the familiar face stimuli again in random order. Participants answered two sequential questions for each face. The first asked whether the given peer provided positive or neutral feedback, with responses anchored in a three-point confidence scale for each valence. The second question assessed the subjective emotional response associated with remembering feedback from a given peer. The latter question used a nine-point Likert scale, where 9 represented the highest possible subjective pleasure and 1 indicated the lowest/ or most unfavorable feeling. Both question's response scales were designed to enhance memory performance, with question 1's scale color-coded to match the original feedback conditions (green for positive, blue for neutral), and emoticons used in question 2 to visually represent the emotional range. To acquaint participants with the complexity of the post-fMRI memory questions, cartoon stimuli were used during instructions.

Image Acquisition. Structural and functional images were acquiring using a Siemens 3T Prisma MRI scanner (Siemens Medical, Germany). High-resolution T1-weighted MPRAGE anatomical images were acquired with the following parameters: TR = 2200 ms, TE = 2.26 ms, flip angle = 8°, field of view = 256 mm, slice thickness = 1.0 mm, and 192 slices. Low-resolution scout images were

acquired to ensure consistent alignment and orientation across anatomical and functional scans. During the acquisition of the MPRAGE images, participants viewed relaxation images.

Functional T2*-weighted images, capturing the blood oxygen level dependent (BOLD) response during the social reward task, were acquired using a gradient echo planar imaging (EPI) sequence with the following parameters: TR = 1100 ms, TE = 30 ms, flip angle = 65º, matrix = 64 × 64, field of view = 192 mm, slice thickness = 3 mm with no inter-slice gap, and a multiband factor of 3. A total of 51 transverse slices were acquired in interleaved order, oriented parallel to the anterior-posterior commissure (AC-PC) line, covering the whole brain.

To minimize discomfort and reduce motion, participants were provided with earplugs and foam padding around their heads. Stimuli were presented using a high-resolution rear-projection system (Avotec, Stuart, FL), and responses were recorded using a fiber-optic response pad (MRA Inc., Washington, PA). Visual stimulus onset time and behavioral responses were recorded by E-Prime (V.2; Psychology Software Tools).

Image Preprocessing. Data were analyzed using FMRI Expert Analysis Tool (FEAT) Version 6.00, part of FMRIB's Software Library (FSL; www.fmrib.ox.ac.uk/fsl). Head motion was corrected using MCFLIRT [129]. Fieldmap-based EPI unwarping was performed using FUGUE [130] to correct geometric distortions in the EPI images. Non-brain tissues for the MPRAGE and EPI images were removed using the Brain Extraction Tool (BET) [131]. Highpass temporal filtering was performed using a Gaussian-weighted least-squares straight line fitting, with a sigma value of 184 seconds, to remove low-frequency noise. Spatial smoothing was applied using a Gaussian kernel with a full width at half maximum (FWHM) of 6.0 mm. Functional images were registered to the high-resolution structural scan using Boundary-Based Registration (BBR), followed by normalization to the MNI template with FLIRT [132] utilizing a 12-parameter affine model.

IV. DATA ANALYSIS

When designing this study, no literature was available to estimate the effect size for AMY-HIP connectivity between PTSD and TRC groups or its relation to symptom severity. A priori power estimates were thus based on memory studies not specifically targeting our regions of interest. One study on emotional working memory in adults with PTSD found an effect size of $R^2 = 0.33$ (Cohen's $f^2 = 0.49$) for the relationship between PTSD severity and average connectivity across a network of regions [133]. Based on this effect size, a general linear model (GLM) with five predictors (group, valence, group × valence), including two covariates would require a sample size of 33 participants (17 per group) to detect differences with 80% power and 5% type I error rate. Another study found a large effect size, with Cohen's d = 0.79 (Cohen's $f^2 = 1.69$) for differences in functional connectivity between PTSD and TRC during working memory tasks [134]. Using the latter effect size, the current study would require 42 participants (21 per group).

Sex was included as a covariate in all analyses given some evidence that stress neurobiology is sexually dimorphic [135]. Sex was limited to being a covariate because the present study is not sufficiently powered to detect sex differences. T-tests, chi-square tests, or their non-parametric equivalents examined group (PTSD, TRC) differences in baseline clinical and demographic characteristics using IBM SPSS Statistics v28. Because no group differences emerged for demographic or clinical characteristics (Table 3) including medications (Table 4), no additional covariates were included in analyses.

Table 3

Measure	Total (n=30)	PTSD (n=12)	TRC (n=18)	p-value
Military Status, n (%)				
Veterans	9 (30.0%)	5 (41.7%)	4 (22.2%)	0.418 [a]
Civilians	21 (70.0%)	7 (58.3%)	14 (77.8%)	
Education, mean years (SD)	-	14.92 (3.09)	16.06 (2.48)	0.291 [c]
Race, n (%)				
White	21 (70.0%)	7 (58.3%)	14 (77.8%)	0.418 [a b]
Black	5 (16.7)	2 (16.7%)	3 (16.7%)	
Asian	2 (6.7%)	1 (8.3%)	1 (5.6%)	
Other	2 (6.7%)	2 (16.7%)	0 (0%)	
Ethnicity, n (%)				
Hispanic	5 (16.7%)	3 (25.0%)	2 (11.1%)	0.364 [a]
Age, mean years (SD)	-	39.08 (8.79)	38.33 (8.53)	0.824 [c]
Tobacco Use, n (%)				
Users	3 (10.0%)	2 (16.7%)	1 (5.6%)	0.548 [a]
Non-users	27 (90.0%)	10 (83.3%)	17 (94.4%)	
Other Substance, n (%)				
Users	4 (13.3%)	3 (25.0%)	1 (5.6%)	0.274 [a]
Non-users	26 (86.7%)	9 (75.0%)	17 (94.4%)	
Sex, n (%)				
Male	8 (26.7%)	3 (25.0%)	5 (27.8%)	1.000 [a]
Female	22 (73.3%)	9 (75.0%)	13 (72.2%)	
ISEL item, mean (SD)	-	1.61 (0.66)	2.30 (0.48)	0.003 [c]

[a] Significance values were derived using Fisher's Exact Tests

[b] Race was classified as white versus non-white race

[c] Significance values were derived using independent samples t-tests

Behavioral Performance. Group differences in recognition memory were assessed using a GLM with repeated measures to account for the within-subject correlation of memory observations. Predictors included diagnostic group (PTSD, TRC), valence (positive, neutral), and group x valence interaction. Sex was included as a covariate. The outcome variable, accuracy, was based on percentage of "HITs" and "Correct Rejections" (CRs) gathered from responses given during the post-fMRI memory task. HITs were defined as responses of 4,5,6 to Mutual- and Received liking conditions (corresponding to successfully remembered positive items); CRs were defined as

responses of 1,2,3 to the ambiguous stimuli (corresponding to successfully remembered neutral items). Accuracy for positive and neutral memories was represented by HITs and CRs divided by total possible favorable- (i.e., 16) and neutral (i.e., 16) stimuli, respectively.

Table 4

Medication Class	**PTSD (n=12)**	**TRC (n=18)**
SSRI, n (%)	4 (33.3%)	3 (16.7%)
SNRI, n (%)	2 (16.7%)	2 (11.1%)
Stimulant, n (%)	3 (25.0%)	2 (11.1%)
Benzodiazepine, n (%)	1 (8.3%)	0 (0%)
Alpha blocker, n (%)	2 (16.7%)	0 (0%)
Antipsychotic, n (%)	1 (8.3%)	0 (0%)
Other Psychoactive, n (%)[a]	3 (25.0%)	0 (0%)
Total Medications count, (mean, SD)[c]	15 (1.25, 1.29)	7 (0.39, 0.61)

[a] n=2 individuals endorsed Bupropion and n=1 endorsed Buspirone

No significant difference was found for any medication class using Fisher's Exact Tests.

[c] There was a marginally significant difference in the distribution of psychiatric medications used between PTSD and TRC groups as determined by a Mann-Whitney U test for continuous data (U = 63, z = -1.88, p = .0601)

Secondary analyses used signal detection theory measures. Sensitivity (d'), measures the distance between signal and noise distribution means in units of standard deviation. In this case, "noise" refers to "False Alarms," or incorrectly recognizing a neutral item as positive [136]. Sensitivity was calculated as Z[HIT] – Z[False Alarms], with a log-linear adjustment applied to accommodate extreme values beyond the normal distribution [137]. Response bias (β) also considers HITs and

False Alarms but is based on an odds ratio to assess the tendency of participants to favor one response over another (e.g., a liberal bias would be a tendency to respond to most items as “rated me favorably” whereas a conservative bias would be a tendency to respond to most items as “did not rate me”) [138].

Secondary analyses also examined confidence ratings from correct post-fMRI recognition responses, transformed into a three-point scale based on the anchors "maybe," "probably," and "definitely." This transformation was done in two steps: first, numerical ratings (1-6) were converted into their respective anchor; second, anchors were reassigned numerical values 1-3 representing increasing confidence. This resulted in original ratings of 1 and 6 becoming a 3 (most/“definitely” confident), original ratings of 2 and 5 becoming a 2 (middle/“probably” confident), and original ratings of 3 and 4 mapping onto a 1 (lowest/“maybe” confident) Additionally, subjective liking ratings (1-9) were analyzed, but only for correctly remembered positive and neutral items, as the study’s aims focused on successful encoding.

Functional Connectivity. Psychophysiological interaction (PPI) analysis [139] was used examine the functional connectivity between the AMY and HIP. Each hemisphere was assessed separately, with the AMY as the seed region and the HIP as the region of interest (ROI). To accomplish this, bilateral AMY seeds were first defined in standard (MNI) space using the Harvard–Oxford probabilistic anatomical brain atlas in FSL, thresholded at 25%. These anatomical regions (right and left AMY) were then co-registered to each participant’s EPI (fMRI) space using FSL’s FLIRT function. Time series data were extracted from these seed regions, giving rise to physiological explanatory variables (EVs) in the PPI analysis. Psychological EVs reflected the subset of items shown during scanning that were later correctly recognized in the post-fMRI memory task (i.e., HITs and CRs). For the sake of the present analysis, memory confidence scores were not considered; all correctly recognized items were treated with equal weighting. Specifically, Ambiguous stimuli identified as

1, 2, or 3 for “Did not rate me” were considered correctly remembered and coded as CRs. Positive memory reflected an aggregate of Mutual- and Received- liking items, as power was insufficient to test the differential value between these conditions. Therefore, responses of 4, 5, or 6 for “This person rated me favorably” were coded as HITs for both Mutual- and Received- liking stimuli. The present study included two psychological EVs: one reflecting the timing of positive (socially-rewarding) items during scanning that were later remembered (i.e., successfully encoded), and the other reflecting the timing of neutral (ambiguous) face stimuli during scanning that were successfully encoded. Psychological EVs were modeled as single impulses convolved with a double-gamma hemodynamic response function.

GLM with local autocorrelation correction was used to calculate parameter estimates for each EV and interaction term as well as any contrasts of parameter estimates (COPEs). Interaction terms reflected the interaction of the AMY time series with psychological EVs. The full PPI model included one physiological regressor, two psychological EVs, and two interaction terms (Hits x AMY, CRs x AMY), with six head motion parameters and head motion outliers (using “fsl_motion_outliers”) included as regressors of no interest. Temporal derivatives and temporal filtering were only applied to psychological EVs. Individual-level statistics were generated in this fashion for each physiological EV (right and left AMY) separately. Seven COPEs were generated in the GLM: HITs, CRs, AMY, HITs x AMY; CRs x AMY; HITs x AMY > CRs x AMY; CRs x AMY > HITs x AMY. Images were thresholded non-parametrically using clusters determined by $Z > 3.1$ and a (corrected) cluster significance threshold of $p = .05$ [140].

To probe functional connectivity (Aim 2), bilateral HIP ROIs were defined using the Harvard–Oxford probabilistic anatomical brain atlas, thresholded at 25%, and then co-registered to each participant’s EPI (fMRI) space using FSL’s FLIRT function. To prevent spatial overlap and inflating ipsilateral time series correlations, the AMY ROI was subtracted from the HIP ROI for each

participant in native space. Next, the corrected HIP ROI was transformed from native space to MNI space for each participant using their own transformation matrix generated during preprocessing. The HIP ROIs in MNI space (left and right separately) were provided as input to FEATquery to extract parameter estimates from PPI interaction terms (HITs x AMY; CRs x AMY; HITs x AMY > CRs x AMY; CRs x AMY > HITs x AMY). To avoid Type I error in functional connectivity analyses, false discovery rate was corrected for two ROIs at $\alpha < .05$.

To test Hypothesis 2a, resultant parameter estimates reflecting AMY-HIP connectivity were submitted to a post-hoc GLM (SPSS v28) which examined the effect of diagnosis (PTSD, TRC), memory valence (positive, neutral), and the group x memory valence interaction. Sex was included as a covariate. To test Hypothesis 2b, analysis was restricted to the PTSD group and PCL-5 score was used as the predictor variable. TRC individuals were excluded from testing Hypothesis 2b because their PCL-5 scores were near the minimum possible value of 0 (Table 5). Including TRC individuals risked introducing a floor effect in symptom severity, which could potentially obscure significant associations observed within the PTSD group.

Table 5

Trauma and PTSD	PTSD (n=12)[a]	TRC (n=18)	p-value[b]
PCL-5, mean (SD)	41.50 (13.2)	8.33 (11.5)	< .001
Lifetime Events Checklist	-	-	-
Total number of traumas, weighted, mean (SD)	19.27 (15.38)	9.00 (5.13)	0.044
Natural disaster, n (%)	8 (72.7%)	12 (66.7%)	1.000
Fire or explosion, n (%)	8 (72.7%)	7 (38.9%)	0.128
Transportation accident (e.g., car wreck), n (%)	10 (90.9%)	12 (66.7%)	0.202
Serious accident, n (%)	7 (63.6%)	5 (27.8%)	0.119
Exposure to toxic substance (e.g., radiation), n (%)	5 (45.5%)	1 (5.6%)	0.019
Physical assault, n (%)	11 (100%)	16 (88.9%)	0.512
Assault with weapon, n (%)	7 (63.6%)	7 (38.9%)	0.264

Trauma and PTSD	PTSD (n=12)[a]	TRC (n=18)	p-value[b]
Sexual assault, n (%)	10 (90.9%)	10 (55.6%)	0.096
Other unwanted or uncomfortable sexual experience, n (%)	10 (90.9%)	11 (61.1%)	0.110
Combat or exposure to a war-zone, n (%)	5 (45.5%)	7 (38.9%)	1.000
Captivity, n (%)	3 (27.3%)	4 (22.2%)	1.000
Life-threatening illness or injury, n (%)	7 (63.6%)	11 (61.1%)	1.000
Severe human suffering, n (%)	6 (54.5%)	7 (38.9%)	0.466
Sudden violent death, n (%)	7 (63.6%)	11 (61.1%)	1.000
Sudden accidental death, n (%)	6 (54.5%)	7 (38.9%)	0.466
Serious injury, harm, or death you caused to someone else, n (%)	4 (36.4%)	4 (22.2%)	0.433
Other traumatic event, n (%)	3 (27.3%)	8 (38.2%)	0.449

[a] One individual is missing a Lifetime Events Checklist. Descriptive statistics and significance levels are calculated with the remaining PTSD sample (n=11)

[b] Significance testing for trauma type was complete using Fisher's Exact Tests. Significance testing for PCL-5 scores and Total number of traumas were conducted using independent samples t-tests

CHAPTER THREE: RESULTS

I. SAMPLE CHARACTERISTICS

Thirty-two participants completed this study. Two participants were omitted from analyses (one due to poor quality of functional images, and the other due to not believing the task design). Both excluded participants were females in the PTSD group. Thus, the final sample was comprised of 30 individuals (N = 12 PTSD). As illustrated in Table 3, the diagnostic groups (PTSD, TRC) included in the final analyses were matched on assessed demographic measures. These included Veteran-status, education, age, race, ethnicity, incidence of tobacco and other substance use, and sex. Nevertheless, sex was included as a covariate in all analyses given some evidence stress

neurobiology is sexually dimorphic [135]. The groups also did not differ by medication use (Table 4). However, they did diverge with respect to PTSD symptom severity (measured by the PCL-5), as expected, and trauma load. Only one traumatic event emerged as being more frequent in the PTSD group, which was the exposure to a toxic substance (Table 5).

Given the literature on social support and PTSD described above, social support was expected to differ between individuals with PTSD compared to individuals without PTSD. This was confirmed with an independent samples t-test using the ISEL average item score between subjects in each group. Individuals with PTSD had lower perceived levels of social support (M = 1.61, SD = .66) compared to TRC individuals (M = 2.30, SD = .48; $t(28)$ = -3.271, 95% CI: [-1.11, -.26] p = .003). Furthermore, there was a large effect size (d = 1.18).

II. GROUP fMRI RESULTS

This study also sought to confirm whether the encoding manipulation of the social reward task promoted BOLD signal change within the brain. To test this, individual statistical maps for each contrast of interest (e.g., HITs, CRs, HITs x L/R AMY) were submitted to group-level analyses using FSL's Local Analysis of Mixed Effects (FLAME). The group-level GLMs included explanatory variables (EVs) for group mean, diagnosis, and sex as a covariate. While no significant voxels emerged for PPI contrasts involving the AMY (e.g., HITs x L/R AMY, CRs x L/R AMY, or comparison contrasts), robust activation was observed for both task-related conditions (HITs and CRs) without the AMY seed, suggesting that successful encoding within the social reward task did drive neurophysiological changes (Table 6). Additionally, a significant effect of diagnosis was found for the HITs > CRs contrast in the medial prefrontal cortex, with greater activation in PTSD compared to TRC individuals (Figure 4). This result is included for thorough data reporting but falls outside the study's focus on AMY-HIP connectivity and is not discussed further.

Table 6

Robust Group Mean Activation or Activation Differences by Diagnosis

Contrast/Region [a]	H [b]	voxels	p	Max Z	x	y	z
HITs vs. Rest [c]							
Occipital Pole	L	24736	<0.001	7.27	-14	-102	10
Parahippocampal gyrus (posterior)	R	7053	<0.001	5.78	22	-30	0
Inferior frontal/pars triangularis	R	2097	<0.001	6.18	50	34	14
Superior frontal gyrus	R	2010	<0.001	5.08	6	18	52
Frontal Pole/mPFC	L	419	<0.001	4.80	-36	50	8
Postcentral gyrus	L	325	0.002	5.21	-56	-18	22
Parahippocampal gyrus (anterior)	R	217	0.014	3.97	6	0	0
Precuneus	R	212	0.015	4.15	6	-58	42
Insular cortex	R	199	0.020	4.40	22	6	10
CRs vs. Rest [c]							
Occipital Pole	L	26887	<0.001	7.28	-18	-100	12
Paracingulate gyrus	R	1331	<0.001	4.72	4	20	50
Middle frontal gyrus	R	685	<0.001	4.78	52	34	20
Orbitofrontal cortex/vmPFC	L	644	<0.001	4.75	-36	24	-4
Precentral gyrus	R	524	<0.001	4.43	44	4	60
Orbitofrontal cortex/vmPFC	R	420	<0.001	5.51	38	26	-4
Parahippocampal gyrus (posterior)	R	326	<0.001	5.71	24	-28	-6
Thalamus	L	170	0.025	4.73	-12	-14	8
Pulvinar	L	153	0.037	5.50	-20	-28	-2
HITs vs. CRs [d]							
Frontal pole/mPFC	L	335	0.003	4.21	-38	62	-6

[a] Anatomic labels provided represent regions of peak activation within each cluster defined by Harvard Oxford Atlas. Coordinates (x, y, z) denoting local maxima are expressed in Montreal Neurological Institute template (MNI) space.

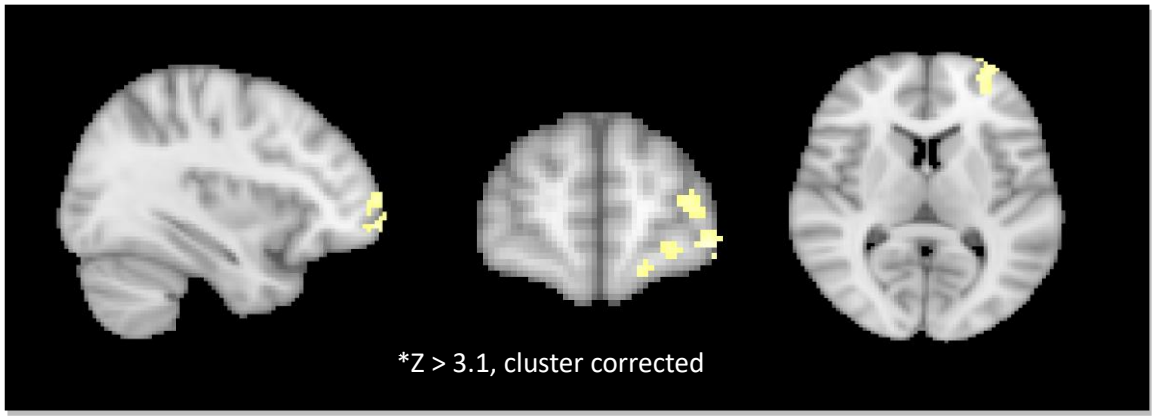
[b] "H" denotes hemisphere

[c] Activation clusters provided for the group mean. "*Rest*" refers to unmodeled time points, including inter-block intervals (IBIs), interstimulus intervals (ISIs), and other task periods associated with unsuccessful encoding that are not explicitly modeled (Misses, False Alarms)

[d] Activation cluster listed for diagnosis group difference (PTSD > TRC)

Figure 4

Group Difference in medial Prefrontal Cortex Response to HITs > CRs Contrast



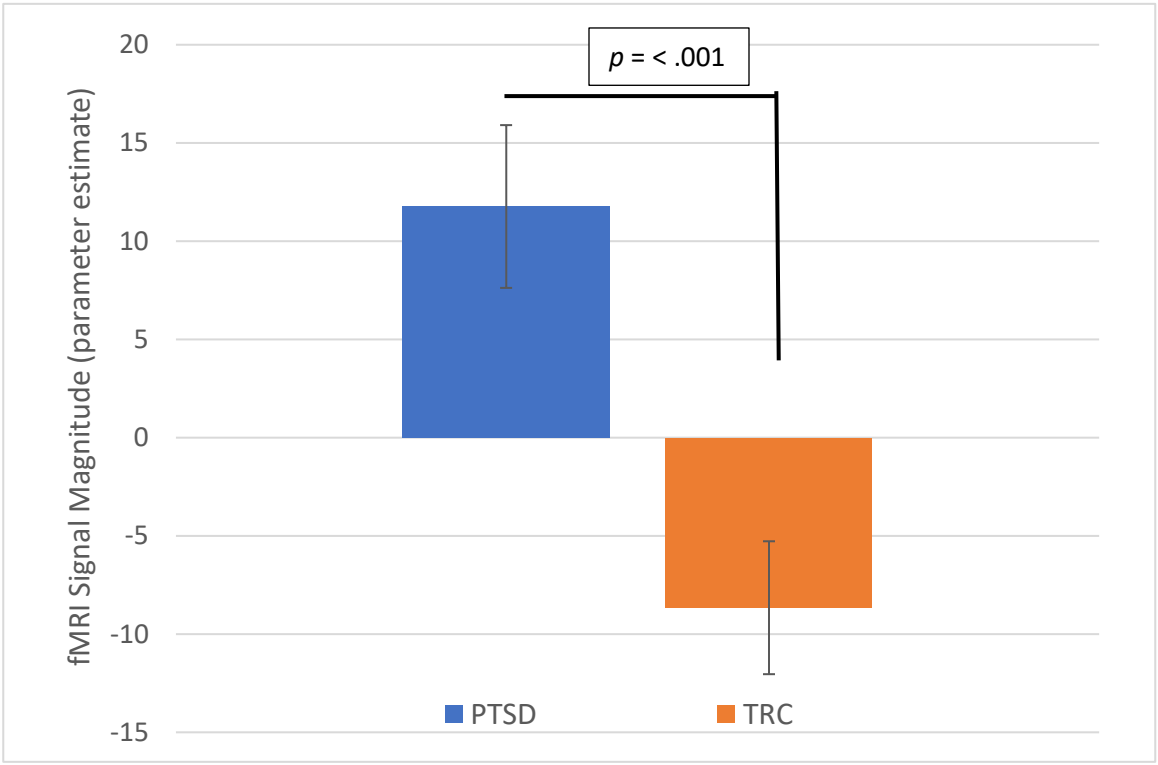


Figure 4. Significant activation cluster detected for a group difference (PTSD vs. TRC) with respect to the HITs > CRs contrast and sex as a covariate. Peak activation falls in an area consistent with the medial prefrontal cortex, extending into the frontal pole. The PTSD group exhibited greater activation for HITs > CRs, while the TRC group exhibited greater activation in the same cluster for CRs > HITs. Error bars represent standard error of mean.

III. BEHAVIORAL RESULTS

The social reward paradigm was designed to assess memory for positive and neutral social stimuli. Neither ceiling effects nor performance at chance-level occurred. The mean accuracy for all successfully encoded events in the full sample was 76.41% (*SD* = 12.95%). With respect to valence, the mean accuracy for HITs (positive memory) in the full sample was 85.20% (*SD* = 12.73%) and 67.71% for CRs (neutral memory; though the scores ranged quite a bit for CRs, *SD* = 21.66%). An independent samples t-test showed that group differences in total accuracy (combined for HITs and CRs) did not differ between PTSD (*M* = 74.87%, *SD* = 9.98%) and TRC groups (*M* = 77.43%, *SD* = 14.80%; *t*(28) = -.565, 95% CI: [-11.82%, 6.71%] *p* = .576. The effect size from this t-test was also small (Cohen's *d* = .20).

Accuracy for Socially Rewarding Memories. Although no differences emerged in overall accuracy between groups, the present study further explored whether recognition accuracy varied by valence within each diagnostic group. Given that social support tends to be reduced in PTSD (a finding replicated in the current sample), Hypothesis 1 predicted an interaction between diagnosis and memory valence, such that individuals with PTSD would show poorer recognition for positive feedback stimuli (HITs) compared to TRC individuals. However, contrary to this prediction, a GLM with repeated measures of memory valence (positive, neutral) did not reveal a significant interaction ($\chi^2(1) = .349$, $p = .555$). Only a main effect of memory valence was observed ($\chi^2(1) = 16.891$, $p < .001$) with higher recognition accuracy for positive compared to neutral items. Estimated marginal means revealed accuracy for HITs and CRs were 84.72% (*SE* = 2.05%) and 67.72% (*SE* = 3.71%), respectively. Figure 5 displays recognition accuracy by valence for each diagnosis, underscoring the main effect of valence.

Figure 5

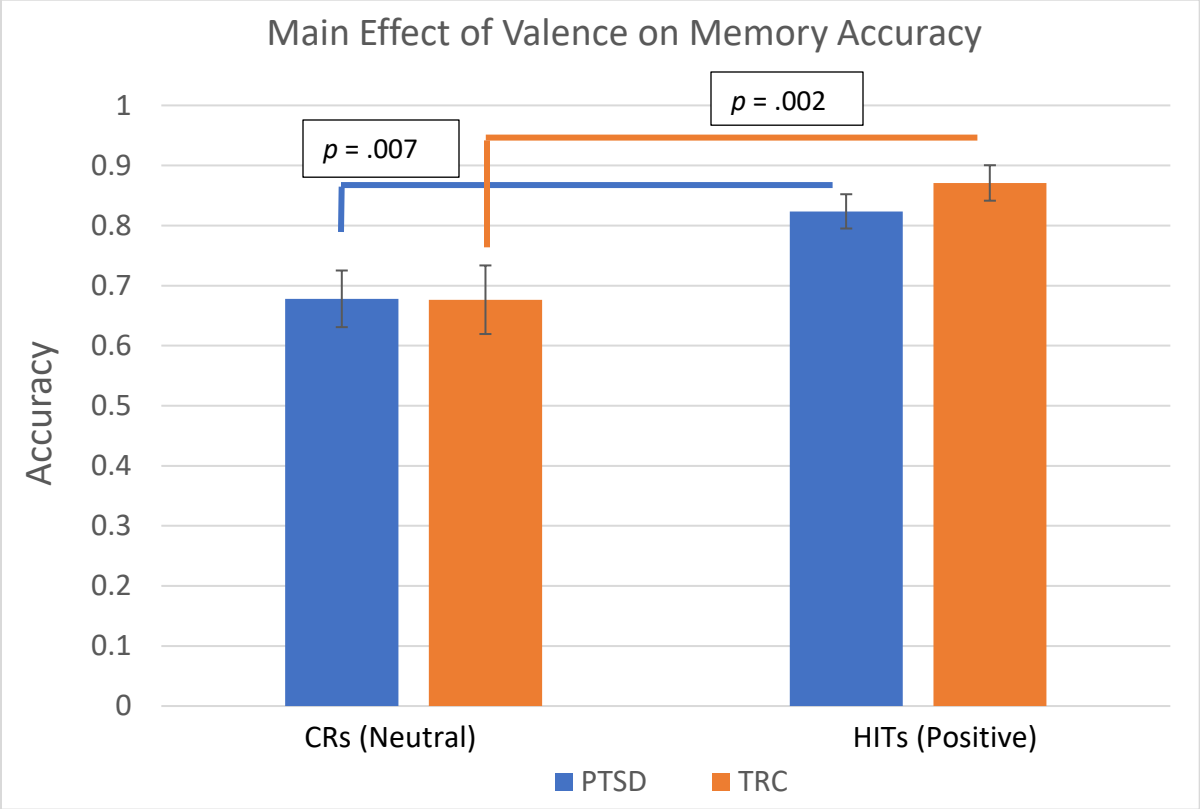


Figure 5. Recognition accuracy for neutral (CRs) and positive (HITs) stimuli in individuals with PTSD and trauma-resilient control individuals (TRC). Although no significant interaction between diagnosis and memory valence was found, a main effect of memory valence emerged, with participants showing higher recognition accuracy for positive compared to neutral items. Estimated marginal means from the GLM with sex as a covariate indicated that HIT accuracy was 84.72% (SE = 2.05%) and CR accuracy was 67.72% (SE = 3.71%). This main effect of valence was observed in both diagnosis groups.

Building on these findings, the present study also examined how specific types of positive feedback—mutual and received liking—affect recognition accuracy. This approach was designed to dissect the broad "positive" valence (HITs) into more specific conditions. The subsequent GLM was constructed in a similar manner as the prior one (i.e., predictors of memory valence, diagnosis, memory valence x diagnosis, and sex) with accuracy as the dependent variable, except

that memory valence had three levels (mutual, received, and neutral). However, this analysis also did not detect an interaction between diagnosis and valence ($\chi^2(1) = .337$, $p = .845$). Again, only a main effect of valence was significant ($\chi^2(1) = 19.215$, $p < .001$). Pairwise comparisons showed that accuracy was greater for mutual ($M = 87.37\%$, $SE = 2.95\%$) versus neutral items ($M = 67.73\%$, $SE = 3.73\%$; $p < .001$) and received ($M = 82.19\%$, $SE = 2.80\%$) versus neutral items ($p = .002$), but accuracy did not differ between the positive condition types, mutual and received ($p = .208$)

Signal detection theory measures. Secondary analyses with signal detection measures of sensitivity (d') and bias (β) were also conducted to better characterize cognitive processes that give rise to mnemonic decision making. The GLM comparing d' by diagnosis and including sex as a covariate revealed no statistically significant group difference in sensitivity ($\chi^2(1) = .941$, $p = .332$; PTSD: $M = 1.42$, $SE = .24$; TRC: $M = 1.72$, $SE = .20$). The absence of a group difference in sensitivity remained even in GLMs with d' restricted to HITs for mutual-liking events ($Z[HIT_{mutual}] - Z[\text{False Alarms}]$; $\chi^2(1) = .422$, $p = .516$; PTSD: $M = 1.50$, $SE = .25$; TRC: $M = 1.71$, $SE = .21$) and d' restricted to HITs for received-liking events ($Z[HIT_{received}] - Z[\text{False Alarms}]$; $\chi^2(1) = .684$, $p = .408$; PTSD: $M = 1.28$, $SE = .24$; TRC: $M = 1.54$, $SE = .19$).

Measures of response bias were also comparable between diagnosis groups. Specifically, there were no diagnosis group differences in the GLM considering all HITs (mutual and received; $\chi^2(1) = .071$, $p = .790$; PTSD: $M = .81$, $SE = .12$; TRC: $M = .77$, $SE = .10$), nor in the GLMs specific to HIT types, mutual: ($\chi^2(1) = .002$, $p = .967$; PTSD: $M = .75$, $SE = .11$; TRC: $M = .74$, $SE = .09$) or received ($\chi^2(1) = .054$, $p = .817$; PTSD: $M = .88$, $SE = .17$; TRC: $M = .93$, $SE = .14$). It can be surmised that neither group exhibited much response bias since estimated marginal means in all cases approached $\beta = 1$, representing no bias.

Confidence in Social Memories. Although no diagnosis effects or diagnosis x valence interactions were observed for recognition accuracy, sensitivity or bias, a secondary analysis was conducted on the outcome measure of memory confidence ratings. A GLM including two levels of valence (positive, neutral) for correctly remembered items, diagnosis, valence x diagnosis, and sex indicated that only valence had a significant effect on confidence ratings ($\chi^2(1) = 12.419$, $p < .001$). Specifically, individuals across both groups (PTSD, TRC) were more confident in their responses given to positive items ($M = 2.41$, $SE = .08$) compared to neutral ones ($M = 2.09$, $SE = 1.00$). Broken down by positive condition type, pairwise comparisons emerging from a second GLM with three-levels of valence revealed that mutual-liking items were rated most confidently ($M = 2.48$, $SE = .08$), followed by received-liking ($M = 2.30$, $SE = .10$), and lowest confidence was found for ambiguous-liking items ($M = 2.09$, $SE = 1.00$). Statistically significant differences were noted, with confidence in memory for mutual- and received- liking events both significantly higher than ambiguous ones ($p < .001$, $p = .046$, respectively). However, confidence in memory did not reach statistical significance between the two positive condition types (mutual and received, $p = .111$), and no interactions with diagnosis were observed.

Subjective Value of Socially Rewarding Memories. While not among the primary Hypotheses, we also sought to confirm that positive items elicited higher subjective liking than neutral items and to determine whether subjective liking differed by diagnostic group. Nine-point valence rating scores for positive and neutral items yielded a two-level within subjects' valence variable, submitted to a GLM as a repeated measure and with diagnosis, valence, diagnosis x valence, and sex as predictors. Successful recognition of positive items (HITs) was associated with greater subjective valence scores ($M = 6.48$, $SE = .22$) than successful recognition of neutral items (CRs) ($M = 5.11$, $SE = .26$), as indicated by a significant main effect of valence ($\chi^2(1) = 20.671$, $p < .001$). Neither the main effect of diagnosis ($\chi^2(1) = 1.436$, $p = .231$) nor the diagnosis x valence

interaction reached significance ($\chi^2(1) = .632$, $p = .427$) (Figure 6). To further address potential differences in subjective value between types of positive stimuli (i.e., mutual vs. received liking), a second GLM was constructed including three valence conditions (mutual, received, and neutral), diagnosis, diagnosis x valence, and sex as predictors. This model again revealed only a main effect of valence ($\chi^2(2) = 58.339$, $p < .001$). However, pairwise comparisons indicated that mutual-liking items were subjectively rated highest ($M = 7.24$, $SE = .23$), followed by received-liking ($M = 5.68$, $SE = .27$), followed by ambiguous-liking ($M = 5.11$, $SE = .26$). Statistically significant differences were noted among stimulus type, with mutual liking rated significantly higher than both ambiguous- ($p < .001$) and received- liking ($p < .001$) conditions. A trend toward significance was observed with higher subjective ratings for received- versus ambiguous- liking items ($p = .082$).

Figure 6

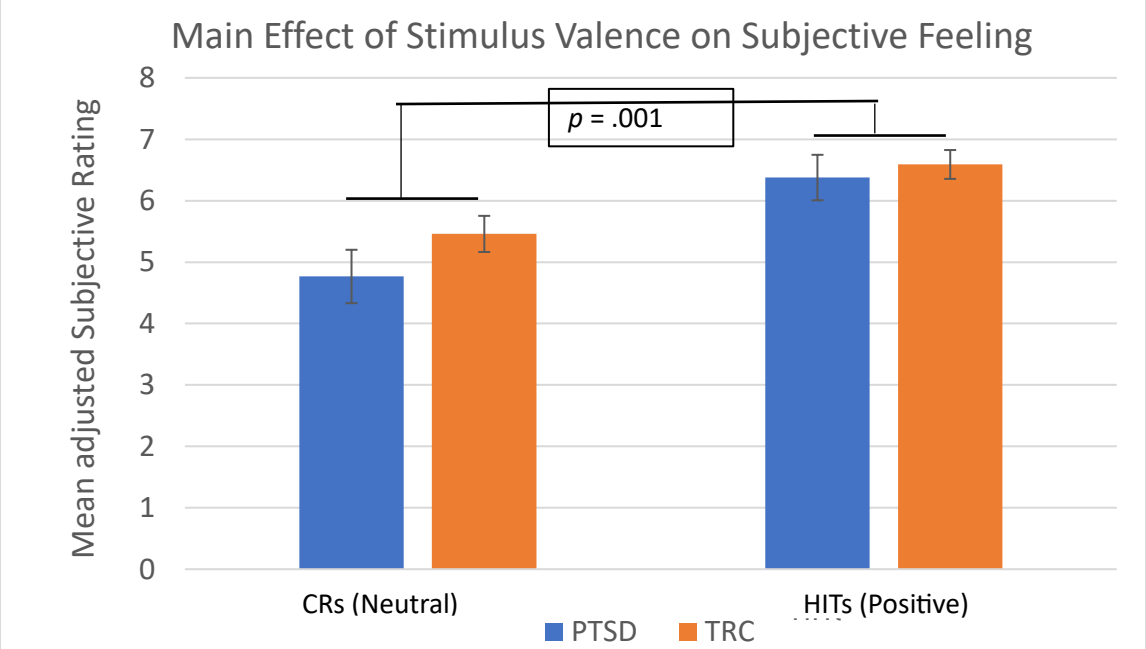


Figure 6. Subjective valence ratings for socially rewarding memories. Ratings for successfully recognized positive (HITs) and neutral (CRs) items were compared among individuals with PTSD and trauma-resilient controls (TRC) individuals. Across both groups, positive memories were associated with higher subjective valence scores compared to neutral memories ($p < .001$). However, no significant differences in valence ratings were observed based on diagnosis ($p = .231$), nor the diagnosis x valence interaction ($p = .427$). Error bars represent standard error of mean.

IV. fMRI CONNECTIVITY (PPI) RESULTS

Hypothesis 2a proposed that AMY-HIP connectivity would be weaker during the successful encoding of socially rewarding events in individuals with PTSD compared to those in the TRC group, considering diagnosis as a binary variable. The GLM examining left AMY-left HIP connectivity, did in fact, reveal a significant interaction between diagnosis and memory valence ($\chi^2(1) = 5.758$, $p = .016$). However, the valence condition embedded in this interaction was not expected since estimated marginal means and pairwise comparisons indicated that this interaction was driven by the neutral memory (CRs) condition. Specifically, the PTSD group exhibited positive AMY-HIP coupling ($M = .064$, $SE = .05$), whereas the TRC group showed negative AMY-HIP coupling ($M = -.049$, $SE = .04$) within the CRs condition ($p = .057$) but no differences were observed for connectivity of HITs ($p = .358$) (Figure 7). The same pattern of results emerged from the GLM using right AMY-right HIP connectivity as the dependent variable. Only a diagnosis x memory valence interaction was observed ($\chi^2(1) = 5.706$, $p = .017$) with the PTSD group showing positive coupling (PTSD: $M = .056$, $SE = .06$) and the TRC group showing negative coupling ($M = -.088$, $SE = .03$). Statistically significant differences in connectivity were found for CRs ($p = .036$) but not for HITs ($p = .983$) (Figure 7).

Hypothesis 2b predicted that AMY-HIP connectivity strength during successful encoding would be negatively correlated with PCL-5 scores within the PTSD group. However, given the results of Hypothesis 2a it was also of interest to test whether neural profiles underlying CRs differed by PCL-5 score. To this end, the GLM treated memory valence as a two-level within-subjects repeated measure and included additional predictors of PTSD symptom severity on a continuous scale, valence x symptom severity, and sex. The initial hypothesis implying a main effect of symptom severity on connectivity was not supported in either the left ($\chi^2(1) = .408$, $p = .523$) or right ($\chi^2(1)$

= .485, p = .486) hemispheres. Additionally, there was no evidence of an interaction between PTSD symptom severity and valence condition in either the left ($\chi^2(1)$ = .619, p = .431) or right ($\chi^2(1)$ = 2.660, p = .103) hemispheres.

Figure 7

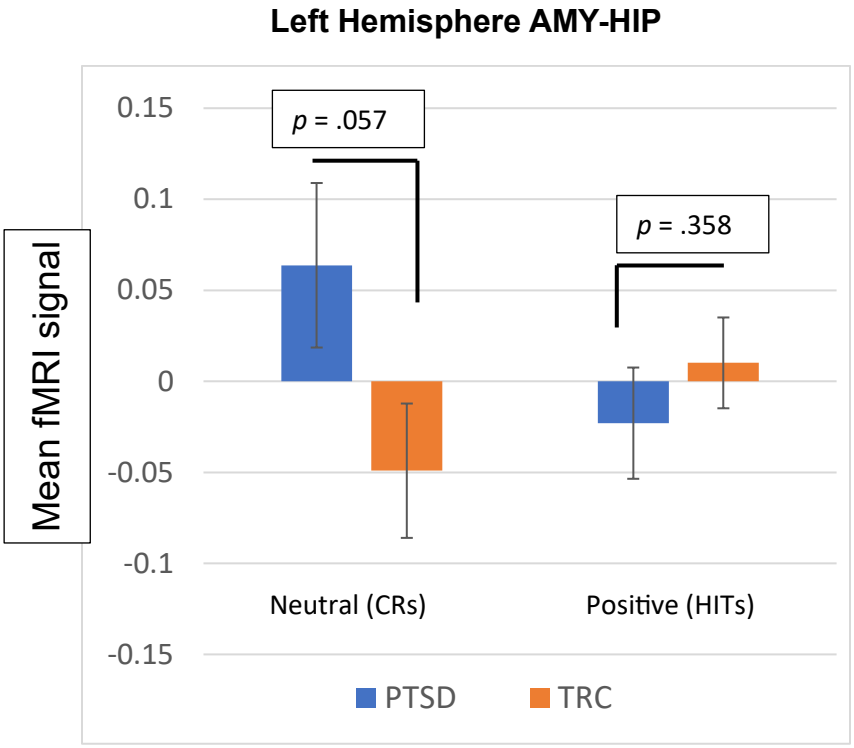
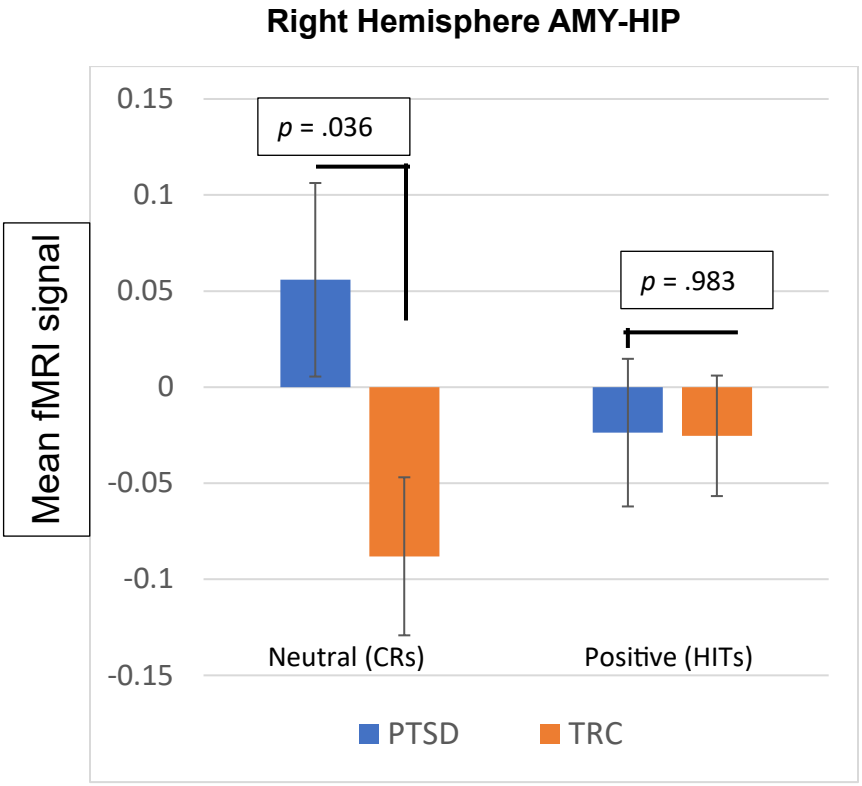


Figure 7. Amygdala-Hippocampus (AMY-HIP) functional connectivity by diagnosis and memory valence. A significant diagnosis x memory valence interaction was found for both left and right AMY-HIP connectivity. Contrary to expectations, this interaction was driven by the neutral memory (CRs) condition. The PTSD group exhibited positive AMY-HIP coupling, while the TRC group showed negative coupling for CRs in both hemispheres. No significant differences were found for HITs in either hemisphere (p > .35). Error bars represent standard error of mean.

Figure 7 (Continued)



With no association between diagnosis or PTSD symptom severity and AMY-HIP connectivity during HIT trials, secondary analyses explored whether behavioral measures during HITs could better explain connectivity variance related to positive memory encoding. Bivariate Spearman correlations revealed no significant association between total HIT accuracy and functional connectivity for HIT trials in either the left (ρ = .014, *p* = .944) or right (ρ = .053, *p* = .783) hemispheres. Similarly, neither loglinear d' nor memory confidence for all HITs were correlated with connectivity in the left (ρ = .199, *p* = .293; ρ = -.050, *p* = .794) or right (ρ = .130, *p* = .493; ρ = -.116, *p* = .542) hemispheres. Lastly, subjective feeling for positive memory items showed no relationship with left AMY-HIP connectivity (ρ = -.021, *p* = .913). While a moderate negative correlation was initially detected for subjective feeling of positive memory items and right hemisphere connectivity (ρ = -.367, *p* = .046; especially for received-liking events [ρ = -.458, *p* = .011; mutual-liking: ρ = -.143, *p* = .451]), this effect did not remain significant when additional

predictors were included in a GLM (diagnosis, diagnosis x subjective rating, and sex; $\chi^2(1) = 1.779$, $p = .182$). Therefore, subjective feeling may contribute to right AMY-HIP connectivity but may also be correlated with another variable, such as sex, leading to shared variance and rendering subjective feeling alone non-significant.

The final secondary analysis explored whether perceived levels of social support could explain variance in AMY-HIP connectivity for HITs or CRs by diagnosis. The rationale followed a similar line of reasoning to Hypothesis 1: It was anticipated that individuals with PTSD, who generally report lower social support, might engage emotional memory encoding networks less robustly than TRC individuals. To test this, a repeated measures GLM was constructed as a full factorial model of valence (positive, neutral), ISEL average item score, the valence x ISEL interaction, and diagnosis, with sex as a covariate, conducted separately for each hemisphere.

In the right hemisphere, a main effect of diagnosis ($\chi^2(1) = 7.308$, $p = .007$) emerged. The estimated marginal means for the main effect of diagnosis indicated that individuals with PTSD have greater (i.e., positive) functional connectivity across successful encoding conditions compared to TRC individuals (PTSD: $M = .010$, $SE = .04$; TRC: $M = -.086$, $SE = .02$). This main effect was further qualified by a marginally significant interaction between diagnosis and social support ($\chi^2(1) = 3.795$, $p = .051$). Specifically, lower perceived social support was associated with enhanced negative connectivity in TRC individuals during successful encoding. Perceived social support moderated connectivity selectively for the TRC group and was not related to connectivity in the PTSD group (Figure 8). No statistically significant three-way interaction between diagnosis, ISEL, and valence emerged in the right hemisphere ($\chi^2(1) = .000$, $p = .988$). In addition, no main effects or interactions were significant for the left hemisphere.

Figure 8

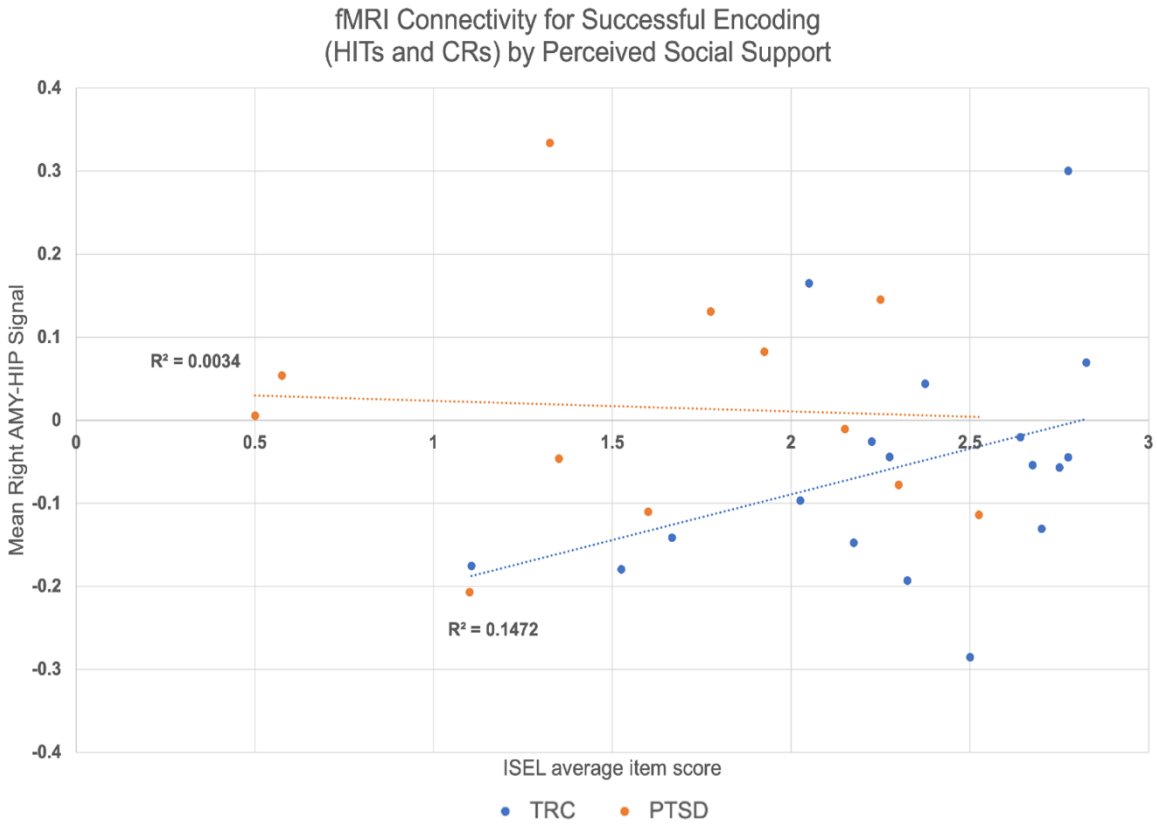


Figure 8. Right amygdala-hippocampus (AMY-HIP) connectivity by diagnosis and social support (ISEL). A GLM testing the relationship between ISEL, diagnosis, and valence on connectivity, revealed a near-significant interaction between diagnosis and social support ($p = .051$). Connectivity across valence conditions (reflecting total successful encoding) was collapsed at the individual subject level and then grouped by diagnosis, to visualize the marginal interaction. Perceived social support may only moderate connectivity among TRC individuals, as there is nearly no relationship between ISEL and mean connectivity among individuals in the PTSD sample. No significant interaction between valence, diagnosis, and social support was detected in either hemisphere ($p > .79$).

CHAPTER FOUR: DISCUSSION

I. SUMMARY

The present study examined (i) whether individuals with- and without PTSD exhibit differences in memory performance for positive versus neutral social events; and (ii) if PTSD versus TRC groups demonstrate differences in AMY-HIP coupling for positive versus neutral social stimuli. The primary hypotheses were that relative to the TRC group, individuals with PTSD would demonstrate both poorer performance in the recognition of positive social stimuli and attenuated AMY-HIP connectivity for positive social stimuli correlating with degree of symptom severity. Contrary to these hypotheses, no behavioral differences were found between the PTSD and TRC groups in recognition memory. In addition, differences in right and left AMY-HIP functional connectivity during memory encoding were observed with respect to diagnosis, but only for neutral items (CRs). In addition, there was no evidence that AMY-HIP connectivity in either memory valence condition was associated with symptom severity in the PTSD group. In other words, diagnostic group moderated left and right AMY-HIP connectivity for encoding neutral social stimuli, but PTSD symptom severity in the PTSD group could not explain variability in AMY-HIP connectivity during memory encoding. These findings are discussed in detail below.

II. COMPARABLE MEMORY PERFORMANCE BETWEEN PTSD AND TRC SAMPLES

Until now, the understanding of positive memory enhancements in PTSD had some limitations. Prior work has (i) neglected positive- and only included negative valence items in tasks (e.g., [53, 116]), (ii) included positive stimuli in their manipulations but did not analyze data within this condition (e.g., [46, 105]), or (iii) collapsed positive and negative items into a single “emotion” condition and/or trauma-exposure (with- or without PTSD) into a single category (e.g., [117, 141]).

The present study addressed this gap and revealed an effect of valence on memory performance. Specifically, memories for salient positive events were preferentially encoded relative to their neutral counterparts in both TRC and PTSD samples. This suggests that trauma exposure, even when it leads to PTSD, does not disrupt the typical bias for positive over neutral memory observed in healthy individuals [90, 117]. This ability to remember positive information in PTSD is surprising given emotional memory tends to be biased toward content affectively congruent with mood [142]. Indeed, a hallmark of PTSD is negative alterations in cognition and mood perpetuating feelings of guilt, shame, anger, and fear [1].

Research shows that the intensity of emotional valence underlies amygdala activation and subsequent memory retrieval in healthy and PTSD samples alike [51, 143]. Given this, the enhancement of emotional memory observed in the present study may be explained by PTSD and TRC groups retrospectively reporting feeling more positive after socially rewarding feedback compared to neutral feedback (Figure 5). Likewise, the lack of a diagnosis x memory valence interaction could be explained by the PTSD and TRC groups having comparable subjective ratings for items correctly remembered in each of the valence conditions (neutral, positive). Evidently, the social reward paradigm previously used in healthy adolescents [125-127], can also invoke positive emotions in adults, including those with PTSD who struggle with emotional numbing [40].

Previous studies have often failed to detect significant differences in memory recognition for positive versus neutral conditions in PTSD and TRC groups [60, 104, 105], but this may be explained by experimental manipulation rather than actual impairments in positive memory. Specifically, many studies rely on generic images from standardized databases, such as the International Affective Picture System (IAPS; [144]), which often do not elicit the intended emotional response—especially for positive stimuli. Subjective ratings for these images are frequently lower than the normative ratings [105, 145], and in some cases, they evoke emotional responses that are

indistinguishable from neutral stimuli [61, 146]. This supports the notion that images inconsequential to the viewer may not impact affect as strongly as more socially or personally relevant ones [147, 148]. By using a more socially meaningful paradigm, like the one employed in the present study, it may be possible to more effectively tap into the emotional and memory processing mechanisms in individuals with PTSD.

Results pointing to comparable subjective measures of social reward between PTSD and TRC groups are worth elaborating because, like memory, literature specifically addressing the perception of *social* reward in PTSD is sparse. Jatzko et al. [107] and Felmingham et al. [108] both used fMRI to interrogate social reward, however the former study did not include a neutral comparison task or subjective measures of affect, so interpretations about reward are constrained. The latter study observed reduced striatal activation for positive > neutral face stimuli in PTSD versus TRC, however PTSD participants also rated happy facial expressions as less positive (more neutral) than TRC individuals, and in general tend to misattribute other emotions to positive stimuli [149]; thus, it is unclear from prior literature whether PTSD interferes with social reward processing *per se* or if the disorder is associated with impairments in labeling emotion (alexithymia) [150]. Because individuals with PTSD in the present study rated positive stimuli as more positive than neutral stimuli, the alexithymia hypothesis would not be supported. Moreover, the present study showed that PTSD does not interfere with memory for face stimuli associated with positive valence, suggesting that psychotherapies that focus on increasing awareness of and sensitivity to socially rewarding cues could potentially boost mood and enhance social integration, addressing key challenges in PTSD treatment.

While the present study's findings suggest that individuals with PTSD do not show an impairment in memory for positive social stimuli and, in fact, rate the stimuli as more positive than neutral stimuli, this should be interpreted with caution. The explicit labeling of stimuli may have

introduced a response bias, where participants rated the stimuli based on valence as designated by the color border rather than genuine emotional engagement.

III. AMY-HIP COUPLING NOT INVOLVED IN POSITIVE MEMORY ENCODING

The premise of the present study rested upon the *memory modulation* hypothesis [151] which predicts that successful encoding of emotional (i.e., positive) items should elicit greater AMY-HIP functional connectivity compared to successful encoding of non-emotional neutral items. This was expected from rodent studies that painted a clear picture of AMY's modulatory influence over the HIP. Specifically, AMY stimulation lowers the threshold for long-term potentiation in the HIP [152], increases the expression of immediate early genes crucial for synaptic plasticity in the HIP [153], and improves memory consolidation during contextual fear conditioning tasks [154]. Further, despite numerous human studies also showing AMY and HIP co-activation at encoding is associated with greater retention of emotional content (e.g., [119, 120, 155]), this was ultimately not replicated in the present study for either group.

Instead, the present study revealed two somewhat contradictory findings. First, when considering diagnosis, valence, the diagnosis x valence interaction, and sex, AMY-HIP connectivity was found to be more pronounced during neutral memory encoding (CRs) than positive memory encoding in both diagnosis groups. The directionality of this coupling differed by diagnosis within the CRs (neutral memory encoding) condition; positive functional connectivity emerged in the PTSD group and negative connectivity was found in the TRC group. Alternatively, when perceived social support (ISEL) was included in a full factorial model with eight predictors, a main effect of diagnosis emerged: individuals with PTSD showed greater (i.e., positive) AMY-HIP connectivity for successful encoding (across both HITs and CRs) compared to TRC individuals. A marginally significant interaction indicated that ISEL moderated connectivity in TRCs but had little to no effect in the

PTSD group (p = .051), suggesting a possible role for social support in AMY-HIP connectivity. Ultimately, since ISEL differed significantly by diagnosis (p = .003), it is likely that ISEL and diagnosis are not independent predictors and captured overlapping variance in connectivity. Given the absence of a three-way interaction between ISEL, diagnosis, and valence, and the marginal ISEL x diagnosis interaction, connectivity interpretations are better aligned with the more parsimonious model, which included only four predictors and where the diagnosis x valence interaction remained significant.

There are several possibilities for why the present study revealed that AMY-HIP was not involved in emotionally positive memory encoding. First, the area defined by the AMY could have been too large, contributing to a diluted effect. The AMY consists of approximately 13 nuclei defined by at least four divisions, Basolateral (BLA), Cortical, Centromedial (CMA), and Other Amygdaloid Nuclei [156]. One study using non-human primates found that only about one-third (specifically 37%) of AMY neurons are selectively responsive to motivationally relevant stimuli [157]. These neurons, which are primarily located within the BLA explain the BLA's distinct role in affective salience [158], social behavior [112], and reward [159]. Further, the BLA is directly involved in memory because it has a monosynaptic projection to both the CA1 and CA3 divisions of the ventral HIP [160]. Emotional memory appears to be specific to the BLA; Administering a glucocorticoid agonist to CMA (rather than the BLA) has no effect on retention in an inhibitory avoidance (a type of fear conditioning) task [161, 162]. Treating the AMY as a single entity, therefore, may mask subregion specific effects.

Another reason the present study may not have detected AMY-HIP activation during positive item encoding is that this synergy is more relevant to encoding *negative* or *anxiety*-related stimuli [163, 164]. Compared to negative memories, the encoding and retrieval of positive information tends to be associated with increased activity in medial and lateral prefrontal regions, as well as midline

areas of the posterior cingulate and precuneus [155, 165, 166]. Indeed, young adults [167] and older adults [168] with stronger post-encoding or resting state medial prefrontal-AMY connectivity tend to show positivity biases in memory. In contrast, encoding profiles heavy in AMY- medial temporal lobe connectivity (including the extended HIP) are associated with memory bias toward negative memories in clinically depressed patients [85]. Compelling evidence suggests that neurofeedback aimed at increasing prefrontal-AMY connectivity during retrieval can enhance access to positive autobiographical memories and alleviate depression symptoms in patients with major depression [169]. Therefore, while AMY-HIP was an appropriate *a priori* circuit to consider given its relevance to memory, future studies comparing *positive* memory encoding profiles between PTSD and TRC individuals should consider prefrontal-AMY circuits. Alternatively, exploring how the AMY interacts with the biological reward system (i.e., ventral striatum), could be a fruitful research avenue because this circuit has been implicated in reward-related learning in healthy adults [170].

Finally, the two reasons mentioned for why AMY-HIP connectivity for positive encoding was missed in the present study could be related. Patel et al. [104] conducted an fMRI experiment interrogating AMY subregion (BLA vs CMA) on emotional memory encoding between PTSD and TRC individuals. Critically, this study was among the few to include positive valence stimuli—and the first to allow a nuanced exploration of the interaction between diagnosis group, AMY subregion, and memory valence. Patel et al. [104] discovered that individuals with PTSD (but not TRCs) expressed greater activation of the BLA versus CMA for negative images > positive images. Additionally, a secondary whole-brain analysis revealed significant activation clusters in the right AMY and right HIP for negative > positive images in the PTSD group. The authors posit that traumatic stress— especially PTSD—may tune BLA and HIP neurons to preferentially respond to negative compared to positive content [171]. However, the extent to which the BLA and HIP

remain intact for positive memory encoding remain uncharacterized because Patel et al. [104] did not report a positive > neutral contrast, and the AMY ROI used in the present study may have been too large to resolve this question. Ultimately, given the relative contribution of the AMY (BLA)-HIP circuit to negative information processing, lack of functional connectivity for positively encoded events and relationship to PTSD symptom severity may not be surprising.

IV. AMY-HIP IS INVOLVED IN NEUTRAL MEMORY ENCODING

The present study found AMY-HIP connectivity in both PTSD and TRC groups for successful encoding of neutral events. Although AMY involvement in non-emotional memory was unexpected, studies have shown the AMY can influence encoding processes in motivationally significant conditions [172], including ones where stimulus meaning is less defined or open to interpretation [173]. Consider the study task: participants were instructed to remember evaluations received from peers. The neutral valence condition depicted the fictitious peer's photograph enclosed by a blue border for 3 seconds. The blue color represented the absence of peer feedback but, nevertheless, was ambiguous because participants could interpret not receiving an evaluation in several ways.

Much like ambiguous words that require contextual clues to interpret, ambiguous stimuli derive meaning from their contexts. However, the ways in which this is accomplished may differ in PTSD and TRCs individuals. The cognitive model of PTSD proposed by Ehlers and Clark [40] states that PTSD is characterized by the inability to view the traumatic event and/or its sequelae as "time-limited," leading to "idiosyncratic negative appraisals" of imminent threat. Consistent with this, studies suggest PTSD-related difficulty in discriminating threat from safety fosters threat generalization [174, 175], contributing to hypervigilance [176], pupil dilation, and increased area of visual scanning [177]. Physiological responses and HIP activation to safe stimuli or safe contexts

in PTSD samples even surface during fear conditioning and extinction when individuals consciously acknowledge that they are safe [178-180]. Accordingly, at least one study also showed that neutral/ambiguous social scenes provoked higher arousal in PTSD compared to TRC samples [181]. Clinical evidence suggests that individuals engage in hypervigilance behaviors to feel safe [177]. Given this, when hypervigilance is activated but no threats are detected, one may expect that anxiety/ negative affect would subside (e.g., negative reinforcement). The absence of a legitimate threat in the present study may explain why subjective ratings of neutral/ambiguous stimuli were not lower in the PTSD group but were instead comparable between PTSD and TRC groups.

Conditioning studies have shown that AMY potentiation can occur when the predictive value of a stimulus is not understood (or has multiple meanings) [182, 183]. This is probably because the AMY monitors salience and activates when the environment is unknown to be safe but, reliably habituates regardless of valence, in animals [184] and healthy individuals [110] once the environment is familiar. However, the AMY does not follow this same pattern in PTSD. Persistent AMY activation in response to repeated presentations of familiar ambiguous stimuli has been observed in those with high post-traumatic stress symptoms, suggesting a neural mechanism that underpins sustained hypervigilance [185]. The present study observed positive coupling between the AMY and HIP in PTSD, which could reflect the AMY's role in promoting threat surveillance and the HIP's role in encoding features of the environment, including features not central to the task, to more thoroughly assess potential threats [186]. Conversely, the negative AMY-HIP coupling observed in TRC individuals may reflect a disengagement of emotional arousal, particularly when it is not needed for neutral information.

This study contributes to the growing body of research indicating that the AMY-HIP circuit plays a role in neutral memory encoding in PTSD [141]. The co-activation of AMY and HIP regions found in previous work, along with the functional connectivity observed here, suggests that emotion-

related memory networks may be inappropriately engaged during neutral memory encoding in PTSD. However, it remains unclear whether increased AMY and HIP activation enhances episodic memory processes or reflects inefficient or compensatory encoding in PTSD, as behavioral performance was comparable between PTSD and TRC groups in both the present and past studies [141]. Future research is needed to explore whether more nuanced aspects of memory, such as vividness, detail, or emotional intensity, are affected by differential AMY-HIP encoding profiles.

V. LIMITATIONS

The present study had several limitations. First, there is a possibility that the present study did not detect AMY-HIP activation in the positive condition because a subset of correctly remembered trials based on low confidence ratings were included. An appropriate subsequent analysis would be to weight BOLD signal by confidence ratings provided on correctly remembered items of the post-scan fMRI task. This way, responses higher in confidence could be represented more than less confident ones with respect to probing AMY-HIP connectivity at encoding.

A second limitation is that time since the index trauma occurred was not considered. This was because there is mixed evidence that memory impairments are related to illness duration. For example, one meta-analysis by Johnsen and Asbjensen [187] suggested an effect of illness duration specifically for verbal memory in PTSD, however their sample primarily included post-Vietnam war Veteran samples with chronic PTSD; hence, decline due to age, predominant male sex, and/or highly comorbid substance use disorders could underlie this memory impairment. Indeed, upwards of 74% of Vietnam Veterans met criteria for co-occurring PTSD and substance use disorder [188]—and alcohol abuse is itself associated with attenuated declarative memory function [37]. Substance use disorders (except mild to moderate cannabis- and tobacco use) were

excluded from the present study to ensure that findings were interpretable for PTSD and TRC samples.

Third, between-group effect sizes in neurobehavioral profiles could have been reduced, or even lost due to the inclusion of psychotropic medications. There is evidence from preclinical studies that treatment with SSRIs reverses HIP atrophy and related HIP-based memory deficits because these medications promote neurogenesis [189]. Additionally, in humans, SSRIs promote negative affect regulation [190], as well as contribute to reduced AMY response to threatening stimuli presented at conscious [191] and pre-conscious levels [192]. Even though the effects of SSRIs on positive/rewarding stimuli are not clear in PTSD, these findings suggest that SSRIs may interfere with the emotional memory network. Future studies are needed to validate if the results reported in the present study remain when medications are accounted for in statistical models or if medication use is exclusionary.

Fourth, like many other studies (e.g., [41, 104, 141]), the present research assessed memory retrieval on the same day as learning. This approach may overlook memory processes that unfold over subsequent hours or days, which could be particularly relevant to memory degradation in individuals with PTSD. Many researchers agree that rapid eye movement (REM) sleep plays a critical role in memory consolidation—the process by which important memories stored in the hippocampus are stabilized and transferred to the neocortex [193]. Given that reductions in sleep quantity and quality are hallmark features of PTSD [1], it is unsurprising that individuals with PTSD often experience fragmented REM sleep [194]. The present study was designed to minimize participant burden and optimize recruitment and retention, so requiring follow-up visits was avoided. However, future research should incorporate delays between study and test phases to capture the impact of sleep and other factors on memory consolidation. There is currently no literature examining the post-consolidation phase of positive memories in PTSD.

A final limitation is with respect to one of the present study's main assessment tools, the PCL-5. The PCL-5 is a widely used clinical tool to track PTSD symptoms and improvement, but it does not probe memory deficits in-depth nor does it probe positive memory. This may be considered a weakness for Aim 2b, as the present study attempted to link neural mechanisms of positive memory encoding to a clinical tool that does not assess for dysfunction of positive memory. There are currently no accepted instruments examining positive memory in PTSD, as this domain of cognitive function has rarely been investigated. However, to partially reconcile this issue, future studies should consider linking the intrusions subscale of the PCL-5 to successful neural encoding of positive memories.

VI. CONCLUSION

Research suggests that access to positive memories, especially those embedded in social contexts, can enhance coping and improve mental health outcomes in individuals with PTSD. Despite deficits in positive autobiographical memory retrieval most often reported in the literature, the present study's findings revealed that individuals with PTSD can subjectively recognize positive events and perceive social reward at levels similar to TRC individuals. This suggests that the neurocognitive mechanisms underlying social reward and memory remain intact in PTSD. Furthermore, this study examined functional connectivity between the AMY and HIP, regions critical for emotional memory. While AMY-HIP connectivity was observed during the successful encoding of neutral memories, its direction differed between groups, with positive coupling in PTSD possibly reflecting pathological hypervigilance behaviors. However, AMY-HIP connectivity did not emerge as significant during the encoding of positive social events. Future research should explore functional subdivisions of the AMY and AMY-cortical connectivity to better understand

the mechanisms underlying social reward encoding, which holds promise for therapeutic interventions in PTSD.

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