The Neural Correlates of Comorbid Depressive Symptoms and PTSD

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Abstract

Individuals with Posttraumatic Stress Disorder (PTSD) often also experience depression. The way people learn and remember things, especially how to differentiate between threatening and safe contexts, may be intricately intertwined with both PTSD and depression. Previous research has utilized fear conditioning paradigms to examine how individuals with these disorders learn to associate and remember that cues can predict threat and safety in different contexts. Previous research suggests that fear-based learning and memory are associated with activation in the hippocampus and amygdala. The purpose of this study was to investigate how activation in these regions during fear memory is associated with severity of depressive symptoms in participants with PTSD. We hypothesized that greater depression symptoms in participants with PTSD would be associated with greater hippocampal and amygdala activation in the safe context and less activation in the threat context. We recruited adults with PTSD and varying levels of depressive symptoms to complete a contextual fear conditioning and memory paradigm during fMRI scanning. Results suggest that individuals with PTSD and more severe depressive symptoms exhibited lower hippocampal activation in the safe context, as well as greater hippocampal activation in the threat context. These findings suggest that higher depression scores are associated with an impaired ability to remember safety in the safe context and to remember threat in the threat context, respectively. Future research should recruit more participants with PTSD and varying levels of depressive symptoms in order to more thoroughly investigate these relationships.

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Introduction

Posttraumatic stress disorder (PTSD) is a psychiatric disorder that affects approximately 3.5% of adults in the United States every year (Torres, 2020b). It is estimated that 9% of people will be diagnosed with PTSD in their lifetime, and this mental illness can cause significant mental, emotional, and cognitive distress (Torres, 2020b). As a result, PTSD is considered one of the top 20 causes of disability in the United States (McKenna et al., 2005). Experiencing a traumatic event such as a natural disaster, serious accident, terrorist act, combat, or physical or sexual assault can lead to PTSD, which often manifests as intense, intrusive, and disturbing thoughts or feelings related to the event, as well as nightmares, flashbacks, startle responses, extreme negative emotions, hyperarousal, difficulty concentrating or sleeping, isolation or estrangement from others, and avoidance of trauma reminders (Torres, 2020b). These symptoms may last long after the traumatic event occurred (Torres, 2020b).

In addition to PTSD, depressive symptoms can also develop following trauma (Torres, 2020b). Depression is a mood disorder characterized by persistent feelings of sadness, loss of interest, changes in appetite and sleep patterns, significant fatigue, feelings of worthlessness or guilt, difficulty focusing or concentrating on tasks, and thoughts of death or suicide (Torres, 2020a). It is estimated that depression affects 6.7% of the general population every year, making it one of the most common mental illnesses in the United States and the world (Torres, 2020a). Additionally, previous reports from the World Health Organization (WHO) project that major depressive disorders (MDDs) could become the leading contributor to the global burden of disease in the coming years (Ferrari et al., 2013). From these statistics, it is clear that depressive symptoms have a significant burden on both individuals and society as a whole.

While depression and PTSD each alone can cause significant distress and impairment in an individual's life, they often co-occur. It is estimated that approximately half of people who suffer from PTSD also meet diagnostic criteria for major depressive disorder, and the presence of depression in people with PTSD can lead to worse outcomes (Flory and Yehuda, 2015). Individuals with comorbid PTSD and depression are more likely to experience reduced life satisfaction, a lower quality of life, and greater severity of symptoms (compared to those with either disorder alone) (Rosen et al., 2020). Additionally, individuals with comorbid PTSD and depression are at higher risk of screening positive for suicidal ideation, as well as at a higher risk

for non-psychiatric illnesses, such as heart disease, migraines, fibromyalgia, and rheumatoid arthritis (Rosen et al., 2020).

The Neural Correlates of PTSD

In the past, much research has been conducted to examine the neural correlates of PTSD. Prior research has observed that PTSD is associated with greater activation in the insula and less activation in the medial prefrontal and anterior cingulate cortices (Liberzon et al., 2009). It is believed that these regions are involved in the development of PTSD symptoms, as they comprise a neural circuit that is implicated in emotional processing and emotional regulation (Liberzon et al., 2009).

Prior research conducted by Bremner et al. (1999) observed differences in fusiform and inferior temporal gyrus and visual association cortex activation, as well as lower hippocampal activation, in response to trauma reminders in women with PTSD who experienced sexual abuse during their childhood. In this study, participants were exposed to personalized childhood sexual abuse event scripts while undergoing positron emission tomography (PET), and blood flow during exposure to these traumatic memories was recorded (Bremner et al., 1999). These findings suggest that dysfunction in these key brain regions may be associated with the perseverance of PTSD symptoms (Bremner et al., 1999).

Additionally, previous studies have shown that the hippocampus and amygdala are key regions affected in PTSD, as these areas are largely responsible for learning and memory processes, especially related to the body's stress response (Bremner, 2006). Specifically, PTSD has been associated with greater cortisol and norepinephrine responses to stress, and this elevated stress response may be associated with common symptoms of PTSD, such as intrusive thoughts, hyperarousal, flashbacks, and startle responses (Bremner, 2006).

Studies investigating learning and memory processing in people with PTSD have found that PTSD symptoms are associated with smaller hippocampal volumes and greater amygdala functioning (Bremner, 2006; Elzinga and Bremner, 2002). A potential explanation for this could be that chronic stress causes hippocampal and amygdala dysfunction (Bremner, 2006; Elzinga and Bremner, 2002). Furthermore, this dysfunction may lead to impairments in memory processing, as observed by deficits in declarative memory, or the memory for facts or events, in individuals with PTSD (Elzinga and Bremner, 2002).

The Neural Correlates of Depression

Depressive symptoms have been associated with differences in dorsal and medial prefrontal cortex, dorsal and ventral anterior cingulate cortex (ACC), orbitofrontal cortex, insula, dorsomedial thalamus, striatum, hippocampus, and amygdala metabolism (Pandya et al., 2012). Although the literature regarding the neural correlates of depression is still growing, and depression's exact effects on these brain regions is unclear, these regions are believed to be implicated in depressive symptoms because they are involved in neural networks involved in problem solving, emotional regulation, cognition, learning, memory, and reward motivation, all of which are affected in individuals with depression (Pandya et al., 2012).

A study conducted by Whalley et al. (2012) observed less activation in the prefrontal cortex during an autobiographical memory task. In this study, individuals with depression were retold personal accounts of a distressing event while inside an fMRI scanner, and their ability to successfully identify personally emotional memories was quantified via brain functioning (Whalley et al., 2012). The findings from this study support the hypothesis that depressed individuals are less effectively able to inhibit task-irrelevant information during a memory task compared to healthy controls, implying the potential association between depressive symptoms and deficits in memory (Whalley et al., 2012).

Another prior study using fMRI technology conducted by Holt et al. (2016) observed differences in medial, temporal, and prefrontal region activation during a self-referential emotional memory task, in which adolescents with MDD were assessed based on their incidental memory for valenced words. The findings of this study support the hypothesis for an association between various differences in brain functioning, depression symptomatology, and deficits in memory and suggest the need for further research to specifically determine these differences (Holt et al., 2016).

Additionally, prior studies have shown that depression is associated with greater hippocampal and amygdala activation during the encoding of negative words, and these findings support the hypothesis that depression is associated with a systematic cognitive negativity bias that creates a hyperreactivity to negative emotion (Ai et al., 2015; Watters and Williams, 2011). In addition, depressive symptoms have been associated with smaller volume and less activation in the hippocampus (Bremner et al., 2000; Shen et al., 2014). It is believed that reduced gray matter volume and lower activation in the hippocampus plays a role in the development of

negative emotions and difficulties in cognitive processing, both of which are hallmark symptoms of major depressive disorder (Zhang et al., 2018).

The Neural Correlates of PTSD and Depression

Combining the findings from studies examining PTSD and depression, prior research suggests that emotional state can significantly impact the way in which information is learned and retained, and because PTSD and depression are both characterized by significant changes in emotional state, hippocampal and amygdala functioning in disorders such as PTSD and depression are important topics of continued research (Richter-Levin and Akirav, 2000).

The hippocampus is thought to be heavily involved in learning, memory, and spatial navigation, whereas the amygdala is thought to be largely responsible for emotions, emotional regulation, motivation, and fear conditioning (Anand and Dhikav, 2012; Wright, 2020). While the brain regions involved in these disorders are well established in the scientific literature, less is known regarding the neural correlates underlying these disorders comorbidly. Since impaired functioning in these areas is associated with the presence of symptoms of both PTSD and depression, a main goal of the current study was to diminish the knowledge gap in this area and to provide insight into whether activation in the hippocampus and amygdala during memory for threat and safety are associated with comorbid PTSD and depressive symptoms (Bremner, 2006; Zhang et al., 2018).

The Relationship Between PTSD, Depression, and Memory

To examine how comorbid PTSD and depressive symptoms impact memory, various prior studies have utilized behavioral and cognitive measures to assess memory deficits in this population. One study conducted by Johnsen et al. (2008) observed that verbal memory was impaired in refugees with PTSD who had been exposed to war or political violence and that this impairment was correlated with depressive symptom severity. These findings suggest that comorbid PTSD and depressive symptoms may be associated with deficits in memory acquisition and encoding (Johnsen et al., 2008).

Another study conducted by Ashbaugh et al. (2016) aimed to quantify the association between PTSD and depression symptoms and the characteristics of trauma memories in a population of undergraduate students with PTSD. Researchers observed that PTSD severity

predicted trauma memories that were more negative, contained higher sensory detail, and were more vivid (Ashbaugh et al., 2016). On the other hand, depression symptom severity predicted trauma memories that were less accessible and less coherent (Ashbaugh et al., 2016). The findings from this study suggest that PTSD and depression influence traumatic memory differently and that further research is needed in order to determine the association between comorbid PTSD and depressive symptoms and memory (Ashbaugh et al., 2016).

As the findings from these studies have shown, PTSD and depression are associated with deficits in multiple types of memory. Therefore, these findings highlight the importance of research into the association between comorbid PTSD and depressive symptoms and memory, as well as research into the hippocampus and amygdala, as those regions are implicated in learning and memory processing.

Hippocampus and Amygdala Function during Memory

Based on the information presented above, the hippocampus and amygdala are key regions in both PTSD and depression, and as a result, they are particularly important to study as mechanisms underlying memory and emotion in comorbid samples. As prior research has implicated hippocampus and amygdala circuitry in regulating learning, memory, and emotion, many prior studies have sought to investigate how these processes are different or impaired in disorders like PTSD and depression (Anand and Dhikav, 2012; Wright, 2020).

Prior research conducted by Bremner et al. (1999) observed reduced hippocampal activation in response to trauma reminders in women with PTSD who experienced sexual abuse during their childhood. In this study, participants were exposed to personalized childhood sexual abuse event scripts while undergoing positron emission tomography (PET), and blood flow during exposure to these traumatic memories was recorded (Bremner et al., 1999). These findings suggest that dysfunction in these key brain regions may be associated with the perseverance of PTSD symptoms (Bremner et al., 1999).

In a different study conducted by Shin et al. (2004), researchers observed greater amygdala function during exposure to traumatic reminders. This study utilized PET technology in Vietnam veterans with PTSD to measure regional cerebral blood flow during the recollection of personal traumatic and neutral events (Shin et al., 2004). The findings of this study support the hypothesis for a positive relationship between activation in the amygdala and PTSD symptom

severity, as well as suggest that dysfunction in key regions, such as the amygdala, are associated with characteristic PTSD symptoms (Shin et al., 2004).

In another study conducted by Milne et al. (2012), researchers observed attenuated hippocampal activation in participants with MDD compared to healthy controls during a memory recollection task. These findings support the hypothesis that hippocampal functioning is impacted by the disease burden of MDD, as well as that memory recollection performance in individuals with MDD may be associated with diminished activation in the hippocampus (Milne et al., 2012). Additionally, these findings suggest that the presence of depressive symptoms may be associated with differences in hippocampal activation and that these differences in hippocampal activation may be associated with recollection memory impairments (Milne et al., 2012).

Taken together, the results of these previous studies suggest that hippocampal and amygdala functioning are associated with deficits in memory. Therefore, more research is needed in order to further examine the association between PTSD and depressive symptoms and specific memory deficits, as well as if and how different types of memory processing are related to hippocampal and amygdala functioning in individuals with comorbid PTSD and depressive symptoms.

The Hippocampus and Amygdala: Neural Underpinnings of Fear Memory in PTSD

One important similarity between PTSD and depression is impaired fear processing (Kemp et al., 2007). The way people learn to differentiate whether they are in a safe or threatening situation is related to how fear is handled in the brain. Specifically, individuals with PTSD often exhibit fear in otherwise safe contexts or environments, such as during firework shows or after an accidental touch (Torres, 2020b).

In order to investigate these symptoms, many studies have used fear conditioning techniques to assess memory for safety and threat. To examine fear conditioning and memory, Milad et al. (2007) observed significant hippocampal activation in response to extinguished versus unextinguished stimuli in the safe context of a fear conditioning paradigm. During this two-day fear conditioning and extinction paradigm, participants exhibited heightened hippocampal and prefrontal cortex activation, suggesting the involvement of the hippocampus and prefrontal cortical regions in extinction memory (Milad et al., 2007). Since this study took

place in healthy participants, this study can serve as a baseline from which studies of fear memory in various mental disorders is based off of.

In one experiment to examine fear conditioning and memory in PTSD, researchers utilized a contextual fear conditioning paradigm in order to investigate how well participants could differentiate between distinct threat and safety cues within different contexts (Garfinkel et al., 2014). To do so, participants were fear conditioned through the presentation of computerized images of library and office scenes, each of which contained lamps that illuminated pink or blue for each trial (Garfinkel et al., 2014). To create a randomly assigned threat context, one light cue in one context (library or office) was paired with a 500 ms shock delivered to the index and middle fingers (Garfinkel et al., 2014). The safe context was created through the presentation of the other context (library or office); however, neither light cue was paired with the shock (Garfinkel et al., 2014).

On the first day of testing, participants were conducted through fear conditioning and extinction learning tasks, which evaluated their ability to remember and differentiate between the threat and safe contexts (Garfinkel et al., 2014). As mentioned earlier, fear conditioning functions through the pairing of a specific context (library or office) with a shock, which created the threat context, so participants were able to learn to fear a certain light cue within a specific context (Garfinkel et al., 2014). After this portion of the study, an extinction learning task occurred. During this task, participants were presented with the other context, and neither light cue was paired with the shock, which created the safe context (Garfinkel et al., 2014). On a subsequent testing day, the threat and safe contexts were re-presented to examine memory for these contexts (Garfinkel et al., 2014). In the extinction recall portion, the safe context was represented, and participants were evaluated on their ability to remember to associate this context with safety (Garfinkel et al., 2014). Afterwards, during the fear renewal portion, participants were re-exposed to the threat context; however, no shock was presented in response to any light cues. Participants were evaluated based on their ability to remember that this context represented threat (Garfinkel et al., 2014).

From this experiment, researchers found that individuals with PTSD were not different from healthy controls during the learning phases (fear conditioning and extinction learning), but they exhibited reduced memory performance (during the extinction recall and fear renewal stages) (Garfinkel et al., 2014). Specifically, participants with PTSD exhibited impaired memory

for safety, as shown by greater skin conductance response (SCR) and amygdala activation in the safe context (extinction recall), as well as impaired memory for threat, as shown by lower SCR and hippocampal and amygdala activation in the threat context (fear renewal) (Garfinkel et al., 2014). Essentially, participants with PTSD exhibited high 'fear' during the safe context (extinction recall), in which no aversive stimulus had been presented, but a lack of expected 'fear' in the threat context (fear renewal), in which the aversive stimulus was presented before (Garfinkel et al., 2014). These results suggest that individuals with PTSD are less effectively able to use context to differentiate between threat and safety cues (Garfinkel et al., 2014). These findings suggest that people with PTSD may have difficulty incorporating contextual information into memory and behavior, which as previous studies have shown, is a hippocampal-dependent process (Rudy et al., 2002).

In another study testing fear conditioning and memory, participants with PTSD exhibited heightened hippocampus and amygdala activation during fear conditioning, extinction learning, and extinction recall tasks (Suarez-Jimenez et al., 2020). These findings suggest that fear overgeneralization may occur in PTSD, as these participants displayed brain activation representative of a hypersensitivity to threat stimuli and contexts (Winters et al., 2021).

In another study conducted by Milad et al. (2009), researchers observed less hippocampal activation during extinction recall in participants with PTSD. The findings from this study suggest that fear extinction may be impaired in individuals with PTSD and that the brain structures, such as the hippocampus, that underlie impairments in fear memory may contribute to the symptoms experienced by individuals with PTSD (Milad et al., 2009).

In another study to test fear conditioning and memory processing in individuals with PTSD, Bremner et al. (2005) observed greater amygdala activation during fear conditioning, an observation that suggests that there is a coordinated network within the brain, including regions such as the hippocampus and amygdala, that is involved in regulating symptoms of PTSD. Similar to other prior research, this study utilized PET technology in a population of women with childhood sexual-abuse-related PTSD to measure cerebral blood flow during the fear conditioning and extinction portions of a fear conditioning paradigm (Bremner et al., 2005). The findings from this study suggest the involvement of the amygdala in fear conditioning and memory, as well as potentially highlight some of the neural correlates underlying an exaggerated fear response in individuals with PTSD (Bremner et al., 2005). This exaggerated fear response

could be associated with the functioning of someone in society, as well as their overall happiness and satisfaction with life (Rosen et al., 2020).

As deduced from the above findings, the literature regarding the association between PTSD and fear conditioning and memory deficits is mixed. For example, some studies observed greater hippocampal and amygdala activation during extinction recall tasks, whereas others observed the opposite association (Garfinkel et al., 2014; Milad et al., 2009). Therefore, more research is needed in order to further understand these associations.

The Hippocampus and Amygdala: Neural Underpinnings of Fear Memory in Depression

On the other hand, previous research has also studied the association between depressive symptoms and fear conditioning and memory. Not many studies have examined fear conditioning and memory in human participants with depression; however, one study found that participants with MDD exhibited impaired fear extinction learning (Kuhn et al., 2014). This study utilized eye-blink startle response, a subcortical output signal that measures threat reactivity during fear conditioning and extinction learning to measure performance in the fear conditioning and memory tasks (Kuhn et al., 2014). Researchers observed that individuals with MDD exhibited normal fear conditioning but enhanced extinction learning, as shown by statistically similar startle responses to both threat and safe contexts during extinction, meaning that the participants had successfully and completely extinguished the fear from fear conditioning (Kuhn et al., 2014). These findings are consistent with the concept that MDD is characterized by greater synaptic plasticity in the amygdala and overarching ventral emotional network, as this enhanced synaptic plasticity may allow individuals with MDD to form an extinction memory more quickly (Kuhn et al., 2014). These findings also suggest the potential success for clinical interventions such as exposure therapy, which has a basis of successful extinction learning, in this disorder (Kuhn et al., 2014).

In another study conducted by Wurst et al. (2021), individuals with major depressive disorder underwent a fear conditioning paradigm, and skin conductance responses, as well as ratings of valence, arousal, and probability of expected threat were measured to quantify fear conditioning and extinction performance (Wurst et al., 2021). Researchers observed that individuals with depression exhibited an impaired ability to learn a conditioned fear, as well as an impaired ability to learn extinction of the conditioned fear after subsequent successful fear

conditioning (Wurst et al., 2021). The findings from this study suggest that MDD impairs fear conditioning and extinction capabilities, as well as that participants with depression were less able to differentiate between threat and safety cues (Wurst et al., 2021).

Taken together, the findings from these previous studies suggest that not only are symptoms of PTSD and depression associated with emotional and declarative memory deficits, but that these symptoms may be specifically related to impairments in fear memory. These results further emphasize that more research is needed to examine the relationship between PTSD, depression, and fear memory. Additionally, while fear conditioning and memory in PTSD and depression have been studied extensively independently, no studies have looked at these processes in individuals with comorbid PTSD and depression. As a result, it is not known precisely how the combination of these disorders is related to fear processing in the brain.

Current Treatments for PTSD and Depression and the Clinical Implications of this Research

Since PTSD and depression affect so many individuals around the world, as mentioned previously, much prior research has been conducted to determine the most effective treatment methods for these mental illnesses. Both of these illnesses greatly impact someone's quality of life and emotional state, and as a result, clinical psychology and neuroscience have attempted to deduce the most effective therapeutic and psychopharmacological interventions.

In the treatment of PTSD, both therapeutic and psychopharmacologic methods have found success in reducing symptom severity and improving someone's overall life satisfaction. Specifically, prolonged exposure (PE), eye movement desensitization and reprocessing (EMDR), and cognitive processing therapies (CPT) all have strong evidence as effective treatments, with PE often being the most effective and common (Sharpless and Barber, 2011; Rauch et al., 2012; Hembree et al., 2003; Shapiro, 2007; Resick et al., 2016). On the other hand, various psychopharmacological interventions have strong evidence as successful treatments as well. Specifically, tricyclic antidepressants (TCAs), monoamine oxidase inhibitors, and selective serotonin reuptake inhibitors (SSRIs) are efficient, with SSRIs emerging as the preferred line of treatment (Albucher and Liberzon, 2002).

Similar to PTSD, both therapeutic and psychopharmacological interventions have strong evidence as effective methods in the treatment of depression. Approaches such as cognitive behavioral therapy (CBT) and psychotherapy have strong evidence as successful for first-line

treatment options for mild depression (Davidson, 2010; Beck, 2011; Frank and Levenson, 2011). In the treatment of more severe depression, psychopharmacological or a combination of psychotherapy and psychopharmacological interventions have strong evidence as the most effective. In particular, second-generation antidepressants, such as SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs), and norepinephrine/dopamine reuptake inhibitors (NDRIs) are often an effective approach (American Psychological Association, 2019). If antidepressants are inadequate, other pharmaceuticals such as antipsychotics or benzodiazepines (only recommended for a short time period) are also occasionally implemented (Davidson, 2010).

Many of the above mentioned methods function through selectively manipulating neurotransmitter response in the brain or by directly attempting to rewire thinking and behavioral patterns, all in an overarching effort to ameliorate symptoms of PTSD and depression. For example, SSRIs, which are commonly used in the treatment of both PTSD and depression, function by restricting the reuptake of serotonin once it is released in the synapse, allowing it to prolong its activity within that brain region (Baudry et al., 2011). Evidence from fMRI studies have observed that SSRI treatment courses attenuated heightened amygdala responses to fearful faces in depression patients, suggesting that SSRIs are associated with mitigating symptoms of dysfunction, such as depression, in the amygdala (Sheline et al., 2001). On the other hand, clinical interventions, such as CBT, function through the attempt to reduce symptom severity through problem-solving to develop helpful coping mechanisms, facing fears rather than avoiding them, and learning to calm the mind and relax the body (American Psychological Association, 2017). Similar to SSRIs, evidence from fMRI studies suggest that CBT attenuated insula and amygdala activation during emotion perception and experience and that this attenuation predicted depression symptom improvement (Gorka et al., 2019). Overall, these treatment methods have the potential to directly impact brain functioning, and evidence suggests that these brain function manipulations are associated with the reduction of symptom severity.

Although these interventions have strong evidence as successful and efficient methods in the treatment of both PTSD and depression alone, PTSD and depression are very frequently comorbid, and these treatment methods do not take that fully into account. As a result, there has not been much research conducted to investigate how to best treat these illnesses simultaneously. The current study has the potential to make important contributions to the field, as an increased

understanding of the neural correlates of comorbid PTSD and depression can influence the development of novel treatment methods and potentially improve overall life satisfaction and quality for individuals suffering from both of these conditions.

The Present Study

The purpose of the current study was to investigate how function in the hippocampus and amygdala is associated with severity of depressive symptoms in participants with PTSD during a fear memory task. This study examined the latter portion of a two-day computerized contextual fear conditioning and memory paradigm in which participants were taught to learn and remember a threat cue. The present study examined solely memory because prior research has suggested that individuals with PTSD exhibit no impairment during learning stages (fear conditioning or extinction), but that they do have deficits in extinction recall and fear renewal (the stages involved with memory) (Garfinkel et al., 2014).

We propose the following overarching aim. Given previous research demonstrating that PTSD and depression are associated with abnormal fear memory processing, we examined whether depression symptom severity was associated with impairments in extinction recall and fear renewal in participants with PTSD (Garfinkel et al., 2014). In order to examine this aim, we propose the following two hypotheses. First, we investigated whether participants with PTSD and more severe depressive symptoms exhibited greater reactivity to threat cues during extinction recall, and as a result, we hypothesized that greater hippocampus and amygdala activation would be associated with more severe depressive symptoms. Second, we examined whether more severe depressive symptoms in participants with PTSD was related to less threat cue reactivity in fear renewal. We hypothesized that lower hippocampus and amygdala activation would be associated with more severe depressive symptoms.

Materials and Methods

Participants

Right-handed adults aged 18-45 were recruited to participate in this study. We recruited participants from the greater Ann Arbor and Metro-Detroit community using University of Michigan's UM Health Research recruitment website, social media advertisements, and flyers

posted around the campus and surrounding community. Participants included in this study were recruited in the context of a larger study examining learning and memory processes in PTSD (full results to be reported elsewhere). The analyses reported here represent secondary analyses of a subsample of the participants from the larger study. Participants were compensated $130 for completing all aspects of this study.

In order for participants to be eligible for the study, they must have been able to give informed consent, and they must have been free of other brain or cognitive disorders. Exclusion criteria included prior diagnosis of a brain disorder; cognitive impairment; learning disability; or neurological disorder (MS, seizure, stroke, tumor, ADHD, etc.); serious head injury; inability to have an fMRI scan; current pregnancy; left-handedness or ambidextrousness; substance use disorder in the last year.

There were 19 participants with PTSD that completed all aspects of the study. 17 (89%) individuals in the cohort identified as women and two (11%) as men. 16 (84%) participants identified as white, one (5%) as black, and two (11%) as other. The cohort had an age range of 19-45 ($M = 26.8$) and the cohort was composed of individuals with depression scores ranging from 0 (minimal) to 50 (severe; $M = 22.2$). However, four participants were excluded from final analysis. One participant was excluded due to bad tissue contrast in the fMRI scans which prevented data processing; one participant was excluded due to missing behavioral data; one participant was excluded because they fell asleep during the tasks; and one participant was excluded due to not completing the fMRI portion of the study.

Following exclusions, we analyzed results from a cohort of 15 individuals who had data for at least one of our tasks. 13 (87%) individuals in the cohort identified as women, and two (13%) identified as men. 13 (87%) participants identified as white, and two (13%) participants identified as other. The cohort had an age range of 19-44 ($M = 25.4$), and participants exhibited depression scores ranging from 0 (minimal) to 50 (severe; $M = 22.8$).

All participants provided written informed consent prior to beginning study procedures, and approval for this study was obtained from the University of Michigan's Institutional Review Board (HUM00121812). Dr. Elizabeth Duval was the authorized principal investigator for this study.

Measures

Participants underwent diagnostic screening to determine eligibility and all participants included in this study had a primary diagnosis of PTSD based on the Clinician Administered PTSD Scale (CAPS) (Weathers et al., 2013). The CAPS is a 30-item diagnostic PTSD assessment interview that evaluates both current and lifetime PTSD diagnosis and symptom severity. Scores range from 0-80, and higher scores indicate greater PTSD symptom severity (Weathers et al., 2013).

Level of depressive symptoms was assessed with the Beck Depression Inventory (BDI) (Beck et al., 1961; Beck et al., 1988). The BDI is a 21-item self-report rating inventory that measures symptoms and behaviors characteristic of depression. Scores range from 0-63, and higher scores indicate greater depressive symptom severity (Beck et al., 1961; Beck et al., 1988).

MRI scanning was performed on a 3.0 Tesla GE Discovery MR750 System (Waukesha, WI) using a state-of-the art 32-channel radiofrequency coil and updated software (Discovery 20.0, Neuro-optimized gradients). T1-weighted anatomic images were acquired with a 3D MPRAGE sequence (FOV = 256 x 256 mm, slice thickness = 1 mm, 0 mm gap). Functional scans consisted of gradient echo blood oxygen level dependent (BOLD) scans with standard parameters across scanners and tasks similar to the following: TR/TE = 2000/30 ms, flip angle = 90 degrees, FOV = 192 x 192 mm, and slice thickness = 3 mm.

Task and Procedure

Participants completed a series of fear conditioning and memory tasks over the course of two consecutive days. The first day consisted of fear conditioning and extinction learning via a computerized contextual fear conditioning and memory paradigm that took place in a mock MRI scanner. The second day consisted of extinction recall and fear renewal via the same computerized contextual fear conditioning and memory paradigm, and these tasks took place in a real fMRI scanner. This fear conditioning and memory paradigm was a modified version of a commonly used paradigm to assess fear learning and memory (Milad et al., 2007; Garfinkel et al., 2014).

Task and Procedure: Day One

Participants were positioned in a mock MRI scanner to simulate a real MRI scan. A recording of an MRI scan was played during the duration of the tasks. A computer screen was viewed through mirrored goggles and participants were given headphones and a button box (with each finger corresponding to a number 1-5) connected to their right hand. Before the fear conditioning paradigm began, participants completed a habituation task in order to become familiar with the stimuli for our task. For this portion, they saw two different contexts (living room and office scenes) that contained light cues. The light cues were presented as different colors of light (orange and blue) that turned on in a lamp fixture. Contexts and cues were counterbalanced across participants, resulting in 4 versions of the task corresponding to the unique combinations of contexts (living room or office) and cues (orange or blue light).

After habituation, the fear conditioning portion of our study began. In the fear conditioning portion, participants viewed one of the two contexts (office or living room) for 2-7 seconds. The light then turned on (either blue or orange) within the context for an additional 2-7 seconds (for a total of 9 seconds per trial). The light cues represented the conditioned stimuli (CS); one light cue was associated with the presentation of an aversive unconditioned stimulus (US; 500 ms loud burst of white noise) in 60% of trials. Thus, participants learned that this light cue was predictive of threat (CS+). The other light cue was never associated with the US and was thus not predictive of threat (CS-; Figure 1a). For example, if the blue light in the living room was associated with the presentation of the burst of loud white noise (US), participants would learn that the blue light was predictive of threat in the living room and therefore to exhibit a fear response when presented with the blue light. On the other hand, as the CS- was never paired with the US, it should not elicit a fear response. From these trials, participants learned to fear one light color, as it predicted the presence of the US, whereas not the other light color, as that signified safety (no US). The inter-trial interval (ITI) was a fixation cross, which was presented in jittered intervals of 4-12 seconds. There were three runs of this task, and 8 CS+ and CS- trials were presented in each run. This task lasted approximately 15 minutes in the mock scanner.

During the extinction portion of the task, participants saw the other context (office or living room; the option not presented during fear conditioning), as well as the two light cues. However, during this phase, neither light was paired with the US, which resulted in extinction of the CS+ (known as CS+E) (Figure 1b). Therefore, during this phase, participants learned that the

CS+ no longer signified threat in this new context. There were two runs of this task, and 8 CS+E trials were presented along with 8 CS- trials in random order within each run. This task lasted approximately 10 minutes in the mock scanner.
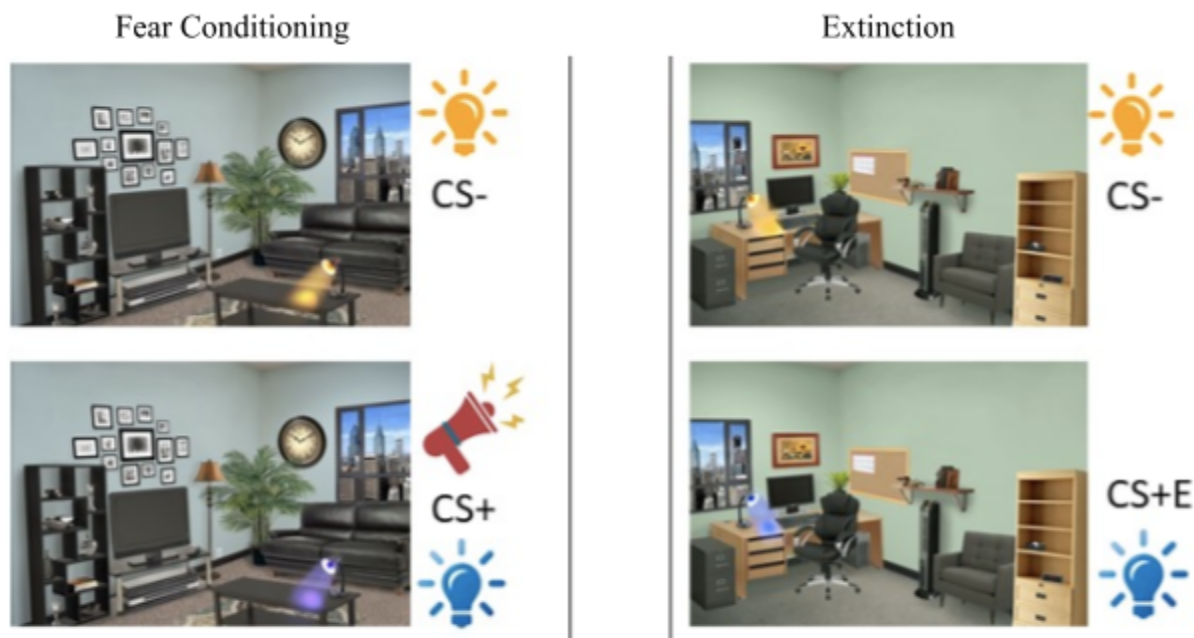

Figure 1a: Example of stimulus presentations during fear conditioning.

Figure 1b: Example of stimulus presentations during extinction.

Task and Procedure: Day Two

        The second day consisted of extinction recall and fear renewal to test participants' memory for the information learned during fear conditioning and extinction. Unlike the first day of the study, this portion of the study occurred in a real fMRI scanner. MRI scans were completed to assess brain activation during extinction recall and fear renewal tasks. A high resolution structural scan was also completed. Most study procedures were identical to the first day. For the second day of the study, participants completed this task by looking at a computer screen through mirrored goggles in the fMRI scanner. Participants were instructed to remain as still as possible and to not fall asleep during the scanning.

        During extinction recall, memory that the CS+E was not predictive of threat in the extinction context (the safe context) was assessed by presenting each of the light cues in the context previously viewed during the extinction phase. This task was conducted to test whether participants remembered that this context is safe (since neither light cue predicted threat in this

context). Similar to the other tasks, participants saw images of the living room or the office with both light cues (orange and blue) (Figure 2a). Participants were once again shown 8 CS+E trials and 8 CS- trials randomly presented in each of two runs. This task lasted about 10 minutes in the fMRI scanner.

During fear renewal, the ability to remember that the CS+ was predictive of threat in the conditioning context (the threat context) was assessed by presenting each light cue (orange or blue) in the room previously viewed in the fear conditioning phase (Figure 2b). This was completed in order to test whether participants were able to remember that this context is threatening (as one light color predicted threat in this context). Once again, 8 CS+E trials and 8 CS- trials were randomly presented within each of two runs. This task took about 10 minutes in the fMRI scanner to complete.

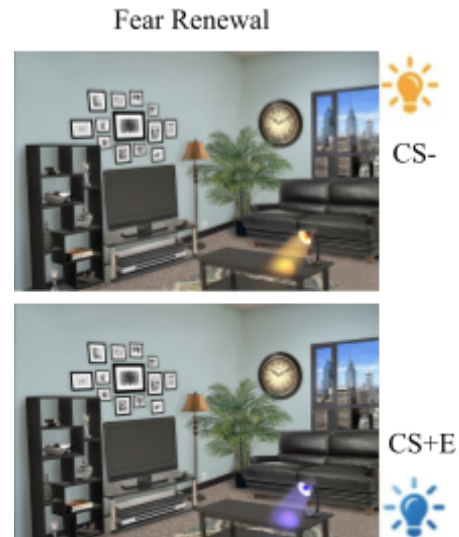Figure 2a: Example of a trial during extinction recall.

Figure 2b: Example of a trial during fear renewal.

Data Processing and Statistical Analyses

To process and analyze the MRI data, we used custom scripts from our lab to run Statistical Parametric Mapping (SPM12) software for MATLAB. Preprocessing of the functional images followed established methods and included slice-time correction, realignment and co-registration to the structural images, normalization to the Montreal Neurological Institute (MNI) standard brain, and smoothing (with a 6mm kernel). Runs with more than 3 mm of motion

in any of the 6 planes (x, y, z, pitch, roll, and yaw) were excluded from analysis. In order to test for preprocessing quality, we conducted quality checks to evaluate image alignment (registration), spatial correspondence (normalization), and motion. Scans that did not pass these preprocessing quality checks were excluded from further analysis.

In order to ensure none of the participants were sleeping during our tasks, we checked for visual cortex activation during trials in which any stimulus was presented compared to implicit baseline (black screen with white fixation cross). Any participants without visual cortex activation during this contrast were excluded from further analysis.

To measure brain activation in the hippocampus and amygdala during extinction recall and fear renewal, activation was quantified for trials that contained a conditioned stimulus (CS) cue that predicted threat (CS+ trials) compared to trials that contained a cue that did not predict threat (CS- trials). In order to evaluate the relationship between hippocampus and amygdala activation and depressive symptom severity in individuals with PTSD, we used correlation analyses. The p-value threshold was set to 0.01 uncorrected, thus results should be treated as preliminary. The dependent measures of the current study included significant BOLD responses in the hippocampus and amygdala.

Results

Extinction Recall (ER)

Neural Activation in the Hippocampus and Amygdala during CS+ vs CS- Trials

To establish activation in brain regions involved in memory for safety, we examined both hippocampal and amygdala activation during CS+ compared to CS- trials during extinction recall. This comparison revealed whether CS+ and CS- cues in the safe (extinction) context were associated with a difference in neural activity. We found that participants exhibited less activation in right (coordinates [x, y, z] = 36, -19, -10) and left hippocampus (coordinates [x, y, z] = -26, -18, -12) during CS+ compared to CS- trials (T = 3.71, p = 0.002; T = 2.95, p = 0.002, respectively) (Figure 3a). In other words, participants exhibited greater activation during trials in

which the aversive US was not presented (CS-) within the safe (extinction) context. There was no statistically significant difference in amygdala activation during CS+ compared to CS- trials.
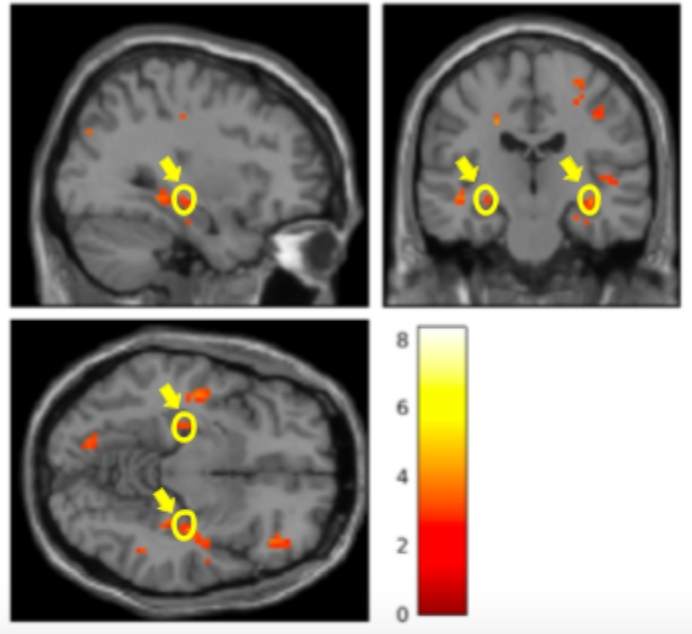

Figure 3a: Greater bilateral hippocampal activity was observed in CS- trials compared to CS+ trials.

Relationship Between Depression Score and Hippocampal and Amygdala Activation

To examine whether activation in the hippocampus and amygdala during extinction recall is associated with depression score, we tested the hypothesis that participants with more severe depressive symptoms would exhibit greater threat reactivity and therefore greater hippocampus and amygdala activation during CS+ compared to CS- trials. Essentially, this analysis quantifies the neural activity in the hippocampus and amygdala during CS+ vs CS- trials, which is the analysis explained above, in relation to depression score. However, contrary to our hypothesis, we found that higher depression scores were associated with less activation of the right anterior hippocampus (coordinates [x, y, z] = 27, -13, -22; T = 3.13, p = 0.005) during CS+ compared to CS- trials (Figure 3b and 3c).
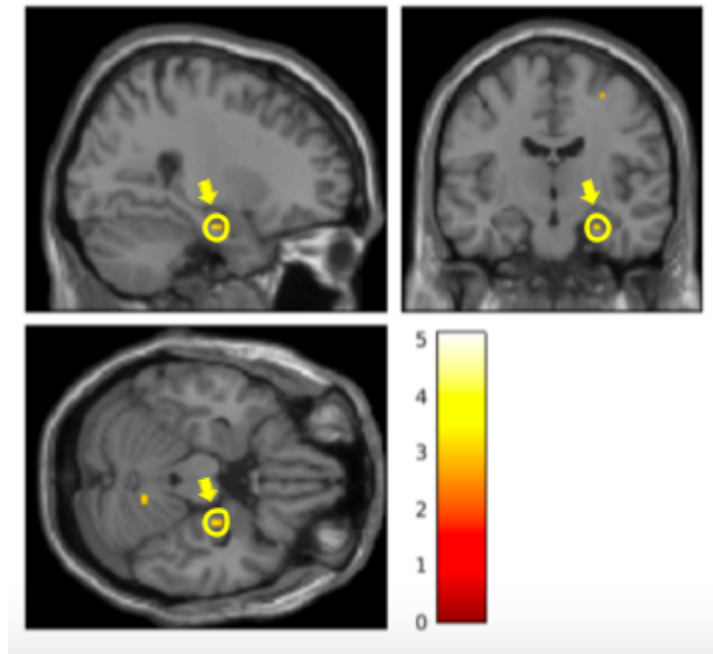
Figure 3b: Unilateral hippocampal activity is negatively correlated with BDI score.
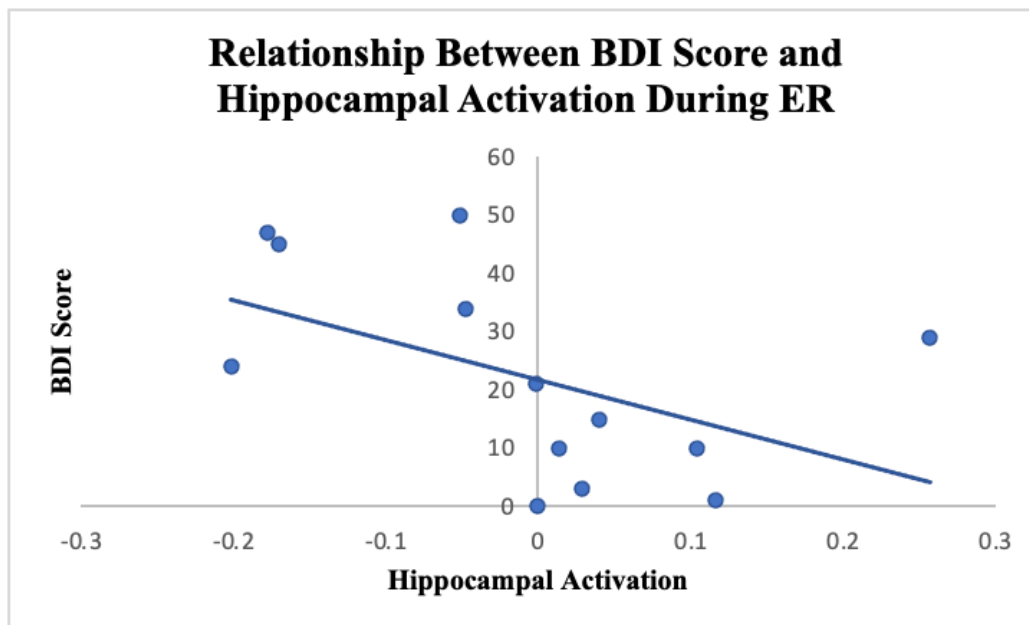

Figure 3c: Negative correlation between BDI score and hippocampal activity during extinction recall

Fear Renewal (FR)

Neural Activation in the Hippocampus and Amygdala in CS+ vs CS- Trials

        To establish activation in brain regions involved in memory for threat, we compared hippocampal and amygdala activation between CS+ and CS- trials during fear renewal. This comparison revealed whether CS+ and CS- cues in the threat (fear conditioning/renewal) context were associated with a difference in neural activity. We found no statistically significant hippocampal or amygdala activation during CS+ trials compared to CS- trials.

Relationship Between Depression Score and Hippocampal and Amygdala Activation

        To examine whether activation in the hippocampus and amygdala during fear renewal is associated with depression score, we tested the hypothesis that participants with more severe depressive symptoms would exhibit lower threat reactivity and therefore lower hippocampus and amygdala activation during CS+ compared to CS- trials. Essentially, this analysis quantifies the neural activity in the hippocampus and amygdala during CS+ vs CS- trials, which is the analysis explained above, in relation to depression score. However, contrary to our hypothesis, we found that higher depression scores were associated with greater activation of the left posterior hippocampus (coordinates [x, y, z] = -24, -31, -4; $T = 3.20$, $p = 0.004$) during CS+ compared to CS- trials (Figure 4a and 4b).
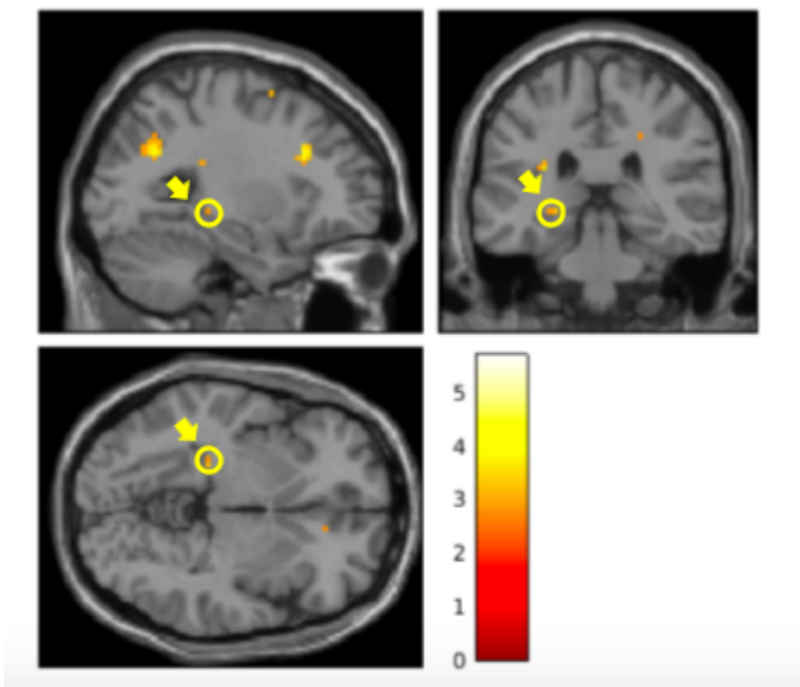
Figure 4a: Unilateral hippocampal activity is
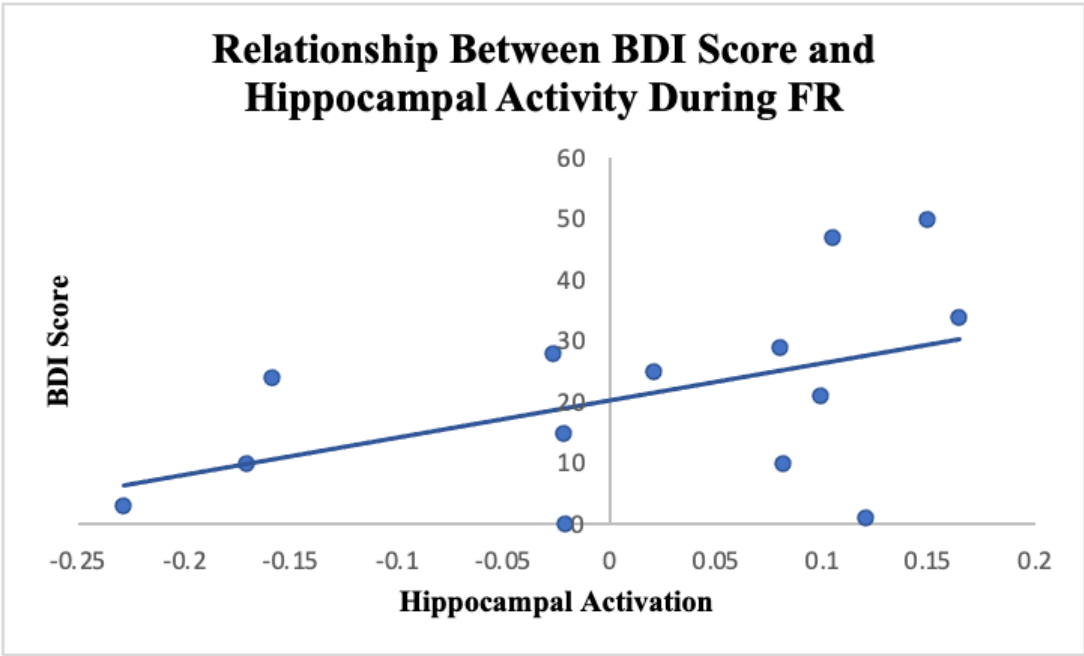positively correlated with BDI score.

Figure 4b: Positive correlation between BDI score
and hippocampal activity during fear renewal

Discussion

Overview

The purpose of this study was to investigate how function in the hippocampus and amygdala underlying fear memory is associated with severity of depressive symptoms in participants with PTSD. We hypothesized that greater depression symptom severity in participants with PTSD would be associated with greater abnormality during extinction recall and fear renewal, and we attempted to quantify this greater abnormality through measuring function in the hippocampus and amygdala using fMRI technology during these fear memory tasks. Specifically, we hypothesized that greater hippocampus and amygdala activation would be associated with more severe depressive symptoms during extinction recall, and we hypothesized that less hippocampus and amygdala activation would be associated with more severe depressive symptoms during fear renewal. Since prior research suggests that individuals with PTSD and individuals with depression oftentimes exhibit exaggerated fear responses and an impaired ability to differentiate between threat and safety cues during fear conditioning and memory, respectively, we hypothesized that comorbid PTSD and depressive symptoms would be associated with these same effects but to an exaggerated level (Rosen et al., 2020; Wurst et al., 2021).

We first examined task-based effects irrespective of depression symptoms to establish activation in the hippocampus and amygdala during CS+ compared to CS- trials for extinction recall and fear renewal. We found that participants with PTSD exhibited less bilateral hippocampal activation during extinction recall trials (the safe context) in CS+ trials compared to CS- trials. These findings suggest that participants with PTSD exhibit less activation in the hippocampus when processing cues that indicated threat in the past but no longer do, as this task took place in the safe context, as well as that the hippocampus is differentially activated during CS+ and CS- trials in individuals with PTSD. Furthermore, these findings may suggest impairments in the complex neural networks underlying memory and emotion, as previous research has shown that individuals with PTSD exhibit deficits in episodic and emotional memory processing (Layton and Krikorian, 2002). As these findings are consistent with prior research conducted by Milad et al. (2009), the findings of the current study suggest that extinction recall is impaired in individuals with PTSD, as well as that brain structures, such as

the hippocampus, underlying these impairments may contribute to symptoms characteristic of PTSD.

On the other hand, these findings are inconsistent with a previous study conducted by Suarez-Jimenez et al. (2020), which observed that individuals with PTSD exhibited greater hippocampal activation during extinction recall tasks, suggesting fear overgeneralization and hypersensitivity to threat cues in individuals with PTSD (Winters et al., 2021). Rather than an overarching fear overgeneralization, the findings from the current study instead suggest that individuals with PTSD may have an impaired ability to utilize contextual cues in situations requiring safety memory processing (Winters et al., 2021; Garfinkel et al., 2014).

Throughout our analyses of the extinction recall portion of our study, we observed no differences in amygdala activation between CS+ and CS- trials in participants with PTSD.

After examining patterns of brain activation to CS+ compared to CS- trials in PTSD, we examined how activation in the hippocampus and amygdala was associated with depressive symptoms. The first hypothesis was that greater hippocampus and amygdala activation would be associated with more severe depressive symptoms during extinction recall. Contrary to our hypothesis, our results suggest that greater depressive symptom severity was associated with less activation of the right anterior hippocampus during CS+ compared to CS- trials. In other words, greater depression scores were associated with less hippocampal activation in the safe context.

Although no prior studies have examined the correlation between comorbid depressive symptoms and fear memory in participants with PTSD, these findings are consistent with some of the prior mixed literature regarding PTSD. As noted by Milad et al. (2009), less hippocampal activation was associated with impaired recall of extinction memory, suggesting that lower hippocampal activation is correlated with impaired fear memory processing. In the case of the current study, perhaps comorbid depressive symptoms in individuals with PTSD is associated with a fear understatement effect, in which these individuals may struggle to retain an extinguished fearful memory even in the safe context. While these findings do not support our hypothesis, they suggest that individuals with PTSD and higher depression scores exhibit lower levels of hippocampal activation during extinction recall and that this reduction in activation may be related to impairments in extinction recall performance (Milad et al., 2009). Furthermore, these findings suggest that comorbid depressive symptoms are associated with impaired fear memory processing in individuals with PTSD and that this is associated with activation in the

hippocampus. Taken together, our findings and those of prior studies highlight the unknown association between comorbidities and fear conditioning and memory processing, as well as the potential association between dysfunction in the hippocampus, safety memory impairments, and PTSD and depression symptoms. More research is needed in order to investigate these relationships.

Next, we examined task-based effects irrespective of depression symptoms to establish activation in the hippocampus and amygdala during CS+ compared to CS- trials for fear renewal. We found no statistically significant hippocampal or amygdala activation during fear renewal trials (the threat context) in CS+ trials compared to CS- trials in participants with PTSD.

The second hypothesis predicted that lower hippocampus and amygdala activation would be associated with more severe depressive symptoms during fear renewal. Contrary to our hypothesis, our results suggest that higher depression scores were associated with greater activation of the left posterior hippocampus during CS+ compared to CS- trials during fear renewal. In other words, higher depression scores were associated with heightened threat reactivity and greater hippocampal activation in the threat context.

Although no prior studies have examined the correlation between comorbid depressive symptoms and fear memory in participants with PTSD, these findings are inconsistent with some of the prior literature regarding PTSD and depression. For example, the study conducted by Garfinkel et al. (2014) observed less hippocampal activation and threat reactivity during fear renewal tasks. One possible explanation for the current findings is that the presence of comorbid depressive symptoms in individuals with PTSD is correlated with a hypersensitivity to threat cues. As noted by Garfinkel and Liberzon (2009), hypersensitivity to threat, as well as hypervigilance and hyperarousal, are hallmark traits of PTSD. Therefore, in the presence of a threat context, individuals with PTSD may be more reactive to remembering the fear, as shown by greater function in the hippocampus during fear renewal. Since our findings support the hypothesis that greater hippocampal activation during fear renewal is positively correlated with depressive symptom severity, they suggest that this hypersensitivity to threat, a hallmark symptom of PTSD, may be associated with depressive symptom severity (Garfinkel and Liberzon, 2009). In other words, hyperreactivity to threat cues, as observed by increased hippocampal activation during fear renewal, may be associated with depressive symptom severity in participants with PTSD.

Another potential explanation could be a general deficit in contextual processing, which is a hippocampal-dependent process, in participants with comorbid depressive symptoms and PTSD (Garfinkel et al., 2014). More specifically, previous research has shown that individuals with PTSD exhibit a reduced ability to utilize safety cues, so it is possible that the greater hippocampal activation observed in participants with comorbid depressive symptoms and PTSD could be related to this overarching difficulty to differentiate between threat and safety contexts (Jovanovic et al., 2012).

In addition to the above inconsistencies, the current findings are also inconsistent with findings from previous studies on depression. A study conducted by Milne et al. (2012) observed that individuals with depression exhibited less hippocampal activation than healthy controls during a recollection memory task. These findings suggest that differences in hippocampal functioning are associated with the presence of depressive symptoms, as well as that differences in hippocampal activation are associated with memory recollection impairments in individuals with MDD (Milne et al., 2012). Although the findings of this study are inconsistent with the findings of the current study, the findings of Milne et al. (2012) were not related specifically to fear memory. Therefore, taken together, the findings of both Milne et al. (2012) and the current study suggest that the presence of depressive symptoms is associated with differences in hippocampal activation and that these differences in activation may be associated with deficits in memory processing. A study conducted by Kuhn et al. (2014) suggested that individuals with depression may have greater synaptic plasticity in the greater ventral emotional network, a network which contains the amygdala and communicates extensively with the hippocampus, and our findings support the idea that this neural network may be more active during fear renewal tasks, which could be associated with the observed increase in hippocampal activation during fear renewal.

Overall, the findings of the current study suggest that individuals with PTSD and higher depression scores exhibit higher levels of hippocampal activation during fear renewal and that this greater activation in the hippocampus may be associated with heightened threat reactivity during fear renewal tasks (Garfinkel et al., 2014). However, as our findings differ with those of the previous literature regarding PTSD and depression, our findings taken together with the prior literature emphasize the unknown relationship between comorbidities and fear memory

processing capabilities. Therefore, more research is needed in order to further investigate these relationships.

Future Directions

  In the future, it would be useful to continue the present study with a goal of recruiting more participants with PTSD and comorbid depressive symptoms. One limitation of our study was the small sample size, as only fMRI data from 15 participants was included in final analyses. Additionally, approximately 90% of our sample identified as white, and approximately 90% of our sample identified as women. Thus, this sample is too small and not diverse enough to reflect the general population. As these data were collected as a subset of a larger, ongoing project, the findings from the current study should be treated as preliminary. However, future studies should recruit a larger sample representative of the general population, with participants identifying with diverse gender and racial identities. This would hopefully allow for a more precise estimate of statistical significance, as well as improved generalizability to the greater population of individuals with comorbid PTSD and depression.

  Another potential future direction could be to look at the relationship between hippocampal and amygdala activation during extinction recall and fear renewal in individuals with comorbid PTSD and anxiety symptoms. Similar to depressive symptoms, anxiety symptoms are also often comorbid with a PTSD diagnosis, and because of this, this avenue for future research could prove very beneficial clinically (Sareen, 2014). For example, this research could contribute to the overarching knowledge base underlying the neural correlates of PTSD and anxiety, and those contributions could impact the development of novel treatment methods for these comorbid conditions. Therefore, future studies could investigate whether anxiety symptoms, in addition to or without comorbid depressive symptoms, are related to impairments in fear conditioning and memory in individuals with PTSD.

  Future research could also look at these relationships in relation to other comorbidities. PTSD is often comorbid with other mental illnesses, such as substance use disorders, and it would be interesting to analyze the association between fear conditioning and memory in individuals with comorbid PTSD and substance use (Roberts et al., 2016).

Conclusions

In summary, the current study aimed to investigate how brain function in the hippocampus and amygdala during fear memory is associated with depressive symptoms in participants with PTSD. Results support the notion that participants with PTSD exhibit impaired extinction recall capabilities, as shown by less bilateral hippocampal activation during presentation of the extinguished threat cue in the safety context. Additionally, the findings from this study suggest that there is a relationship between depression symptom severity and brain function during fear memory, as shown by lower hippocampal activation to a previously threatening cue within a safe context and greater hippocampal activation to a previously threatening cue within the threat context. Differences in hippocampal activation associated with depression may suggest impaired fear memory.

These results provide preliminary findings that contribute to our understanding of the neural mechanisms underlying fear conditioning and memory in people with PTSD and depression. This knowledge may aid in future studies investigating the association between comorbid mental illnesses and brain functioning. Additionally, these findings highlight the importance of research on the neural mechanisms of comorbid mental illnesses, as there may be a confounding or even exponential association between comorbid symptom severity and overall brain functioning. As PTSD, depression, and a plethora of other mental illnesses impact the livelihood and happiness of countless individuals around the world, understanding the neural functioning underlying comorbid mental health conditions has multiple potential clinical implications (Rosen et al., 2020). This research can contribute to treatments that are better positioned to address multiple conditions and therefore have immense impacts on treatment effectiveness, as well as overall wellbeing for individuals with comorbid mental health conditions.

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