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Review Article

PTSD-related neuroimaging abnormalities in brain function, structure, and biochemistry

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ABSTRACT

Although approximately 90% of the U.S. population will experience a traumatic event within their lifetime, only a fraction of those traumatized individuals will develop posttraumatic stress disorder (PTSD). In fact, approximately 7 out of 100 people in the U.S. will be afflicted by this debilitating condition, which suggests there is substantial inter-individual variability in susceptibility to PTSD. This uncertainty regarding who is susceptible to PTSD necessitates a thorough understanding of the neurobiological processes that underlie PTSD development in order to build effective predictive models for the disorder. In turn, these predictive models may lead to the development of improved diagnostic markers, early intervention techniques, and targeted treatment approaches for PTSD. Prior research has characterized a fear learning and memory network, centered on the prefrontal cortex, hippocampus, and amygdala, that plays a key role in the pathology of PTSD. Importantly, changes in the function, structure, and biochemistry of this network appear to underlie the cognitive-affective dysfunction observed in PTSD. The current review discusses prior research that has demonstrated alterations in brain function, structure, and biochemistry associated with PTSD. Further, the potential for future research to address current gaps in our understanding of the neural processes that underlie the development of PTSD is discussed. Specifically, this review emphasizes the need for multimodal neuroimaging research and investigations into the acute effects of posttraumatic stress. The present review provides a framework to move the field towards a comprehensive neurobiological model of PTSD.

1. Introduction

Posttraumatic stress disorder (PTSD) is a debilitating mental health condition that affects approximately 7 out of 100 people in the United States population (Kessler et al., 2005). The disorder is characterized by persistent cognitive-affective dysfunction that develops as a result of exposure to a traumatic event (American Psychiatric Association, 2013). Patients with PTSD experience recurrent, intrusive, and involuntary thoughts or memories of their traumatic experience. Further, these patients often exhibit heightened arousal and increased emotional reactivity, which may manifest as hypervigilance or an exaggerated startle response to potential threats. PTSD patients also avoid thoughts, behaviors, and situations that are associated with the traumatic event. In addition, these patients show negative alterations in cognition and mood that include a diminished ability to express positive emotions and distorted negative beliefs about themselves. Finally, the PTSD symptoms that have been described may occur with dissociative symptoms (i.e., a dissociative subtype of PTSD) that include depersonalization (e.g., feeling as if one is outside their own body) and derealization (e.g., feeling as if things happening outside oneself are unreal or unfamiliar). Thus, trauma exposure and the resulting posttraumatic stress can disrupt cognitive-affective processes that are important for healthy emotional function. Importantly, nearly 90% of the United States population will experience some type of traumatic event in their lifetime (Breslau et al., 1998; Kilpatrick, 2013). However, only a fraction (e.g., ~10–20%) of those exposed to trauma go on to develop PTSD (Kessler et al., 1995). Further, posttraumatic stress symptoms are highly variable over time, making it difficult to determine who will develop PTSD (Bonanno and Mancini, 2012). Given the high rate of trauma exposure and the uncertainty surrounding who will develop PTSD, it is critical to develop comprehensive models of posttraumatic stress that can effectively predict an individual's risk for

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the disorder. Effective predictive tools would inform early intervention efforts to lessen the economic, social, and emotional burden of the disorder. Thus, a key goal of ongoing research is to identify the underlying pathophysiology of PTSD. To this end, recent advances in neuroscientific research have identified brain circuitry that appears to play an important role in the cognitive-affective dysfunction linked to PTSD.

PTSD is characterized by disruptions in cognitive-affective processes that support healthy emotional function (American Psychiatric Association, 2013). A key component of healthy emotional function is the ability to adaptively respond to threats in the environment. For example, one can mitigate potential harm by avoiding or defending against an imminent threat. These defensive behaviors are promoted by signals that warn one that the threat is imminent (i.e., stimuli or events that precede the threat). The formation, expression, and extinction of fearful associations between warning signals and the threats they predict are important emotional learning and memory processes that are critical for healthy emotional function (Domjan, 2005; Goodman et al., 2018; Harnett et al., 2016, 2017a; LaBar et al., 1998; LeDoux, 2000; Maren, 2001; VanElzakker et al., 2014). These fear learning and memory processes are mediated by a brain network centered on the prefrontal cortex (PFC), hippocampus, and amygdala (Fig. 1).

Prior neuroscience research suggests that PTSD is mediated by dysfunction of the neural circuitry that supports fear learning and memory processes (Bremner et al., 1995; Milad et al., 2009; Shin et al., 2001). Specifically, the PFC, hippocampus, and amygdala appear to play a key role in the cognitive-affective dysfunction associated with PTSD. In fact, previous work has identified functional, structural, and biochemical alterations within the PFC, hippocampus, and amygdala of PTSD patients (Bremner et al., 1995; Fani et al., 2016; Milad et al., 2009; Pitman et al., 2012; Yang et al., 2015). Therefore, these brain regions are potential targets for further translational neuroscience efforts focused on predicting and preventing the development of trauma and stress-related disorders. However, gaps in our current knowledge limit the development of comprehensive neurobiological models of these disorders. In the current review, we identify findings from neuroscience research that elucidate the neurobiology of trauma and stress-related disorders. We describe the neural substrates that support healthy emotional function and highlight findings across several magnetic resonance imaging (MRI) modalities from prior PTSD research that has demonstrated alterations in the function, structure, and biochemistry of these brain regions. This review discusses the benefit of multimodal neuroimaging investigations for characterizing the neural substrates of PTSD. Further, we note the need for future studies of recently trauma-exposed individuals, which will advance our understanding of the neural processes that mediate PTSD susceptibility. The present review provides an overview of the neurobiology of PTSD and presents a framework for further investigations into this disorder.

2. Neurobiology of fear learning and PTSD

The PFC, hippocampus, and amygdala form a neural network that mediates fear learning and memory processes and regulates expression of the peripheral emotional response (Fig. 1). The basolateral amygdala (BLA) encodes stimulus information and plays a critical role in the formation of associations between warning signals and the threats they predict (Campeau and Davis, 1995; Fanselow and Kim, 1994; LeDoux et al., 1990). Projections from the BLA to the central nucleus of the amygdala (CeA) mediate the conditioned expression of the peripheral emotional response (e.g., freezing, startle, and skin conductance responses) (Avery et al., 2014; Cheng et al., 2003, 2006; Dong et al., 2001; Helmstetter, 1992; Helmstetter and Bellgowan, 1993; Knight et al., 2005; LaBar et al., 1998; Maren, 2001; Ono et al., 1985; Pitkänen et al., 1997; Veening et al., 1984; Weller and Smith, 1982; Wilensky

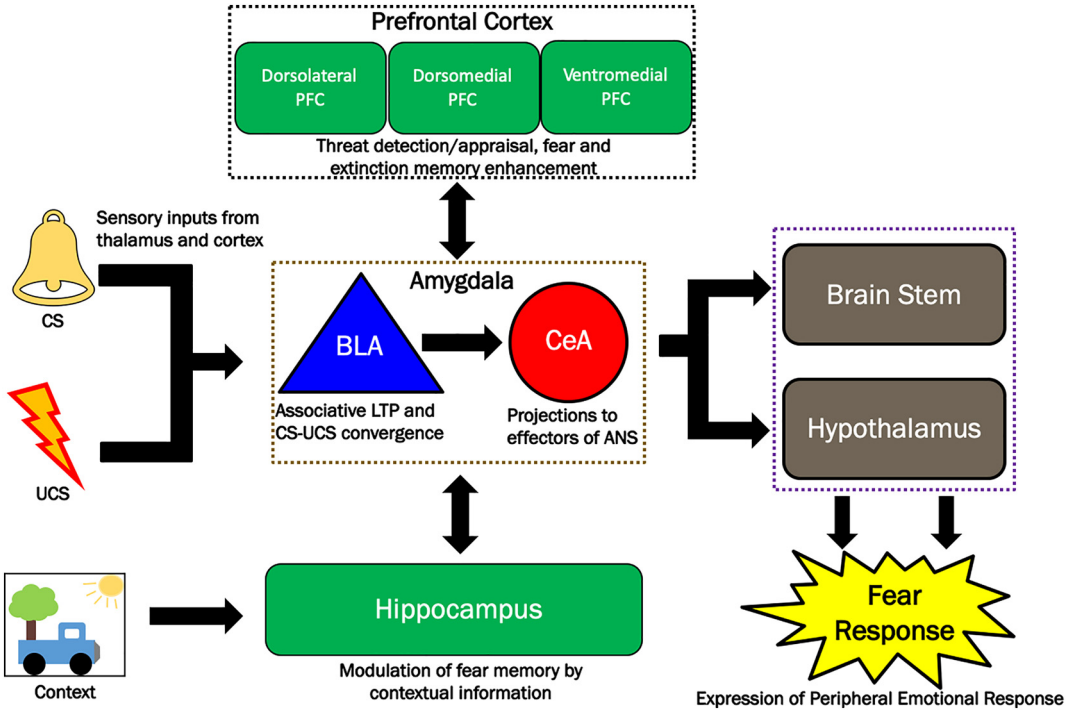

Fig. 1. Schematic overview of fear learning. The prefrontal cortex (PFC), hippocampus, and amygdala form a network critical for the acquisition and expression of fear memories. Sensory information about the conditioned stimulus (CS) and unconditioned stimulus (UCS) are passed via cortical and subcortical routes to the basolateral nucleus of the amygdala (BLA) which mediates acquisition of the CS-UCS association via long-term potentiation. The central nucleus of the amygdala (CeA) receives information on the CS-UCS association from the BLA and has downstream projections to effectors of the autonomic nervous system (ANS), such as the brain stem and hypothalamus, to elicit peripheral expression of the fear response. Contextual information related to the CS and UCS (e.g., stimulus timing, environment) are utilized by the hippocampus to modulate fear memory formation. Further, the dorsolateral PFC, dorsomedial PFC, and ventromedial PFC support threat detection, appraisal, and inhibition processes necessary for dynamic modulation of fear memory expression.

et al., 2006). Thus, the amygdala is critical for the formation of fear-related associations and the expression of emotional behaviors in anticipation of an impending threat. These amygdala-mediated learning processes are regulated via projections from other brain regions that include the hippocampus, dorsolateral PFC, dorsomedial PFC, and ventromedial PFC. The hippocampus supports temporal, contextual, and declarative memory processes that are important for predicting threatening stimuli (Haritha et al., 2013; Harnett et al., 2016, 2017a; Marschner et al., 2008; McEchron et al., 1998; Phillips and LeDoux, 1992; Selden et al., 1991), and uses declarative knowledge of temporal and contextual information to develop conscious expectations of impending threats (Haritha et al., 2013; Knight et al., 2004; Knight et al., 2009). These threat-related expectations are projected to the dorsolateral PFC which allocates anticipatory, attentional resources towards threat-relevant stimuli (Bishop et al., 2004; Bishop, 2009; Clarke et al., 2014; MacDonald et al., 2000). Information about threat-relevant stimuli then passes to the dorsomedial PFC. The dorsomedial PFC compares threat-related expectations to the threats that are actually encountered, which is a critical aspect (i.e., error detection) of associative fear learning (Carter et al., 1998; Carter and Van Veen, 2007; Li and McNally, 2014; Ridderinkhof et al., 2004). Further, the ventromedial PFC serves to regulate the emotional response to the threat itself (Goodman et al., 2018; Motzkin et al., 2015; Urry et al., 2006; Wood et al., 2012). Together, the processes supported by the PFC, hippocampus, and amygdala are responsible for healthy emotional function.

Fear learning and memory processes are disrupted in PTSD. Disruption of these processes interferes with patients' ability to regulate the emotional response. Although PTSD patients are able to form associations between warning cues and subsequent threats, these patients tend to overgeneralize learned fear associations to non-threatening stimuli (Bremner et al., 2005; Grillon and Morgan, 1999; Harnett et al., 2018a; Inslicht et al., 2013; Rabinak et al., 2017). Specifically, PTSD patients express emotional responses and expect threats in the presence of non-threatening stimuli (Fani et al., 2013; Grillon and Morgan, 1999; Rabinak et al., 2017). Further, PTSD patients show difficulty reducing the emotional response once a warning cue no longer signals threat. For example, PTSD patients often show impairments in fear extinction processes (Garfinkel et al., 2014; Milad et al., 2008, 2009). Together, the behavioral evidence suggests PTSD disrupts fear learning and memory processes such that stronger and more rigid fear responses are inappropriately expressed to non-threatening stimuli.

PTSD appears to be mediated by the dysfunction of a PFC-hippocampus-amygdala network. Given that fear learning and memory processes are disrupted in PTSD, alterations within the PFC, hippocampus, and amygdala may underlie development of the disorder. In fact, a number of prior neuroimaging studies have investigated these brain regions to better understand the neurobiology of PTSD (Fani et al., 2016; Milad et al., 2009; Olson et al., 2017; Pennington et al., 2014; Shin et al., 2009; Stevens et al., 2013). This prior work suggests PTSD is associated with alterations in the function, structure, and biochemistry of the PFC, hippocampus, and amygdala.

2.1. Function

The amygdala is a critical component of the neural circuit that supports fear learning and memory. Specifically, the amygdala supports the formation of fear-related associations between warning signals and the threats they predict. Further, the amygdala is necessary for the conditioned expression of the peripheral emotional response (Cheng et al., 2003, 2006; Knight et al., 2004, 2005; LaBar et al., 1998). However, PTSD patients show impairments in the fear learning and memory processes that are supported by the amygdala (Blechert et al., 2007; Grillon and Morgan, 1999; Jovanovic et al., 2010). Amygdala activation is often elevated in PTSD patients compared to controls, suggesting PTSD is linked to amygdala “hyperactivity” (Hayes et al., 2012; Patel et al., 2012). Amygdala “hyperactivity” may mediate, in part, the emotional dysfunction that characterizes PTSD. Specifically, amygdala “hyperactivity” may facilitate associative fear learning, resulting in stronger fear associations that are more prone to generalization and are more difficult to suppress.

Hyperactivity of the amygdala and the overexpression of the emotional response in PTSD may be mediated by dysfunction of the ventromedial PFC. The ventromedial PFC is a key component of the fear learning and memory network. Specifically, the ventromedial PFC is critical for regulation of amygdala activity and suppression of the fear response (Milad et al., 2007b; Motzkin et al., 2015; Urry et al., 2006). Thus, ventromedial PFC dysfunction may lead to the heightened emotional reactivity and extinction learning deficits observed in PTSD. Consistent with this view, prior research has observed diminished ventromedial PFC activity in PTSD patients compared to controls during emotional tasks (Garfinkel et al., 2014; Hayes et al., 2012; Rougemont-Bücking et al., 2011). The reduced ventromedial PFC activation may underlie PTSD patients' failure to suppress fear responses (Milad et al., 2009). Thus, PTSD appears to be associated with ventromedial PFC “hypoactivity”, which may reflect a failure to suppress amygdala activation and may, in turn, disrupt fear learning and memory processes.

An important caveat to the prior findings of amygdala “hyperactivity” and ventromedial PFC “hypoactivity” is that these patterns of activation may be specific to a typical PTSD presentation. Prior investigations of the dissociative subtype of PTSD have observed ventromedial PFC “hyperactivity” and amygdala “hypoactivity” (Hopper et al., 2007; Lanius et al., 2010). One possibility is that the amygdala-ventromedial PFC findings within the dissociative subtype of PTSD are related to the overregulation of the emotional response. This hypothesis is consistent with prior work that found that those with the dissociative subtype of PTSD showed a smaller physiological response to emotional events compared to individuals with a more typical presentation of PTSD symptoms (Lanius et al., 2001; Lanius et al., 2002; Seligowski et al., 2019). Thus, while PTSD is generally associated with overexpression of the emotional response, the dissociative subtype of PTSD may be related to an underexpression of the emotional response.

Dysfunction of the dorsolateral and dorsomedial PFC also plays an important role in the disrupted fear learning and memory that is observed in PTSD. The dorsolateral and dorsomedial PFC support the formation and expression of learned fear responses (Knight et al., 2004; Knight et al., 1999; Milad et al., 2007a). Notably, dorsolateral PFC activity is attenuated in PTSD patients during anticipation of emotional stimuli (Aupperle et al., 2012). This diminished dorsolateral PFC activation is related to greater PTSD symptom severity (Aupperle et al., 2012). Further, PTSD patients show heightened dorsomedial PFC activity during both fear acquisition and extinction recall (Milad et al., 2009; Rougemont-Bücking et al., 2011). Increased activity within the dorsomedial PFC may underlie the formation of stronger fear associations that are more resistant to extinction. Of note, however, there may be differences in the dynamics of dorsal PFC activity between PTSD phenotypes. For example, functional connectivity from the dorsolateral PFC to the amygdala is greater in those with the dissociative subtype of PTSD than those with typical PTSD presentations (Nicholson et al., 2015). These findings may reflect the increased top-down control of amygdala-mediated emotional expression processes, which is consistent with the view that the dissociative subtype of PTSD is associated with overregulation of the emotional response. Taken together, this prior work suggests that there are important differences in the type of dorsolateral and dorsomedial PFC dysfunction that underlies distinct types of PTSD, which may explain the heterogeneity of PTSD symptoms. Further, these findings more broadly demonstrate that these brain regions are important for understanding PTSD-related dysfunction.

Hippocampal dysfunction is also common in PTSD and appears to mediate important fear learning and memory deficits. The hippocampus is critical for the formation of conscious threat expectations that facilitate associative fear learning (Haritha et al., 2013; Knight et al., 2004,

2009). Importantly, PTSD patients show difficulties in the formation of threat expectations and other declarative memory processes (Bremner et al., 2004; Rabinak et al., 2017; Tischler et al., 2006). Further, PTSD patients show reduced hippocampal activity during fear learning and other declarative memory tasks (Carrión et al., 2010; Hayes et al., 2011; Milad et al., 2009). Thus, PTSD is associated with reductions in hippocampal activity that appears to underlie the disruption of fear learning and memory processes.

2.2. Structure – gray matter

Changes in brain gray matter may be another neurobiological process that underlies the dysfunction of fear learning and memory in PTSD. In fact, several studies have observed gray matter alterations within the PFC, hippocampus, and amygdala in PTSD patients (Karl et al., 2006; Kühn and Gallinat, 2013). This prior research has demonstrated both volumetric (e.g., gray matter volume) and morphological (e.g., gray matter surface area and thickness) differences between PTSD patients and controls in these regions.

Prior research suggests the amygdala and hippocampus are susceptible to stress-induced changes in brain structure (Ding et al., 2010; Magarinos et al., 1997; Mitra et al., 2005; Vyas et al., 2002). For example, stress exposure can lead to the remapping of neuronal connections (Mitra et al., 2005; Vyas et al., 2002). Stress also appears to lead to the death of neurons within the amygdala and hippocampus (Ding et al., 2010; McEwen, 1998). However, the findings of prior research on changes in hippocampal structure in PTSD patients have been mixed. Although several prior studies have observed smaller hippocampal volumes in PTSD patients (Bonne et al., 2008; Bremner et al., 1995; Bremner et al., 1997), other studies have noted that hippocampal volume differences are inconsistent or that these differences may be compounded by other factors (Karl et al., 2006; Smith, 2005; Woodward et al., 2006a). Interestingly, a recent large-scale meta-analysis found evidence of smaller hippocampal volumes in PTSD (Logue et al., 2018). Reductions in hippocampal volume also vary with PTSD symptom expression such that as hippocampal volume decreases, the severity of PTSD symptoms increases (Gilbertson et al., 2002; Villarreal et al., 2002). Posttraumatic stress is also related to reductions in the volume of the amygdala (Ganzel et al., 2008; Rogers et al., 2009). Given neural activity within the amygdala and hippocampus support fear learning and memory processes, alterations in the structure of these brain regions may underlie the emotional dysfunctional observed in PTSD. Interestingly, structural alterations in the hippocampus may be a neurobiological characteristic that is common across many of the distinct types of PTSD. Prior work in individuals with PTSD - both with and without the dissociative subtype, as well as individuals with PTSD and dissociative identity disorder - show similar reductions of hippocampal volume in comparison to healthy controls (Chalavi et al., 2015a, 2015b; Daniels et al., 2016). The similarity of these findings (i.e., across distinct PTSD subtypes) highlights the consistency of stress-related changes in hippocampal volume across different presentations of PTSD. Taken together, the present literature suggests stress disrupts the health of the amygdala and hippocampus, reducing the volume of these brain regions, which play an important role in PTSD.

Stress-related morphological changes within the PFC also appear to play an important role in PTSD. Prior work demonstrates that neurons within the PFC are vulnerable to stress (Radley et al., 2004). Similar to the amygdala and hippocampus, stress can lead to neuronal changes within the PFC (Liston et al., 2006). In fact, several studies have reported differences in the gray matter of the PFC in PTSD patients compared to controls. Specifically, PTSD patients show reduced gray matter volume within the dorsomedial PFC (Rauch et al., 2003; Woodward et al., 2006b; Wrocklage et al., 2017; Yamasue et al., 2003). Further, PTSD is associated with reduced gray matter volume and cortical thickness of the ventromedial PFC (Bing et al., 2013; Li et al., 2014). These findings suggest posttraumatic stress reduces the gray matter of the PFC. Importantly, the structural morphology of the PFC is directly linked to fear learning and memory processes (Milad et al., 2005; Milad et al., 2007a; Winkelmann et al., 2016). In particular, the thickness of the dorsomedial and ventromedial PFC is linked to fear expression and extinction processes. Thus, stress-induced structural changes within the PFC may contribute to the disruption of fear learning and memory processes that have been observed in PTSD patients.

2.3. Structure – white matter

Disruptions in the structural connections between the PFC, hippocampus, and amygdala also appear to play an important role in PTSD. Specifically, the microstructure of the cingulum bundle, uncinate fasciculus, and fornix/stria terminalis may underlie important aspects of the pathophysiology of PTSD (Fani et al., 2015; Fani et al., 2019; Harnett et al., 2018a; Kennis et al., 2015; Koch et al., 2017). These white matter tracts connect brain regions that are critical for fear learning and memory processes, and thus variability in the microstructure of these tracts may mediate the emotional dysfunction associated with PTSD.

The dorsomedial PFC and ventromedial PFC are connected by the cingulum bundle. Therefore, the cingulum bundle supports functional interactions that are necessary for fear learning and memory processes. As noted above, PTSD patients show disruptions in the function and gray matter structure of the dorsomedial and ventromedial PFC (Bing et al., 2013; Garfinkel et al., 2014; Milad et al., 2009; Woodward et al., 2006b). These functional and structural disruptions are linked to the subsequent dysfunction of fear learning and emotion regulation processes. Therefore, emotional dysfunction may be linked to the microstructure of the white matter that connects these brain regions. Specifically, disruptions in the white matter microstructure of the cingulum bundle may partially mediate the deleterious effects of posttraumatic stress on emotional function. Prior studies have demonstrated diminished white matter microstructure of the cingulum bundle in PTSD patients (Fani et al., 2016; Sanjuan et al., 2013). Further, the microstructure of the cingulum bundle varies negatively with expression of the peripheral emotional response and the severity of PTSD symptoms (Fani et al., 2015; Harnett et al., 2018a). These findings suggest the cingulum bundle is associated with the emotional dysfunction observed in PTSD. Thus, weaker structural connections between the dorsomedial and ventromedial PFC (i.e., the cingulum bundle) may play an important role in the emotional dysfunction observed in PTSD.

Similar to the cingulum bundle, the uncinate fasciculus is an important white matter tract for emotional function given it connects the ventromedial PFC and amygdala. Importantly, PTSD patients often show “hyperactivation” of the amygdala and “hypoactivation” of the ventromedial PFC (Hayes et al., 2012). Changes within the uncinate fasciculus may partially underlie these dysfunctional neural patterns by constraining the ventromedial PFC's regulatory control over the amygdala, resulting in the dysregulated emotional expression observed in PTSD patients. Several recent reports have observed reduced uncinate fasciculus microstructure in PTSD patients (Koch et al., 2017; O'Doherty et al., 2018; Olson et al., 2017). Interestingly, the microstructure of the uncinate fasciculus was observed to vary both positively and negatively with PTSD symptom severity (Costanzo et al., 2016; Harnett et al., 2018a; Koch et al., 2017). The different findings observed across these studies may be partially related to differences in the specific metric of white matter microstructure used in these prior projects. Fractional anisotropy and mean diffusivity are separate but complementary metrics of white matter microstructure, where the former is an index of the overall directionality of water diffusion and the latter is an index of the overall diffusivity of water within a brain region. In the prior research, mean diffusivity of the uncinate fasciculus varied positively with PTSD symptom severity (Koch et al., 2017) while fractional anisotropy of the uncinate fasciculus varied negatively with PTSD

symptom severity (Costanzo et al., 2016; Harnett et al., 2018a; O'Doherty et al., 2018). Together, these data suggest the white matter health of the uncinate fasciculus decreases as posttraumatic stress severity increases. Thus, the microstructure of the uncinate fasciculus may partially mediate the impact posttraumatic stress has on amygdala and ventromedial PFC function. Taken together, the current literature suggests that alterations in the microstructure of the uncinate fasciculus contribute to the emotional dysfunction observed in PTSD.

Microstructural changes in the fornix/stria terminalis may also play an important role in the emotional dysfunction observed in PTSD. The stria terminalis supports the peripheral expression of the emotional response by connecting the amygdala to deep-brain nuclei that include the hypothalamus. It is important to note that conventional human neuroimaging methods often cannot entirely separate the stria terminalis from the fornix, which connects the hippocampus to the hypothalamus (Mori et al., 2008, 2017). Thus, human neuroimaging studies must often make inferences about both the fornix and stria terminalis in combination. However, limited research has investigated the microstructure of the fornix/stria terminalis in PTSD patients. Prior work in non-PTSD populations has found a positive relationship between the microstructure of the fornix/stria terminalis and trait anxiety (Modi et al., 2013). These data suggest the microstructure of the white matter pathway that connects the amygdala and hypothalamus plays an important role in emotional function. Interestingly, reductions in the microstructure of the fornix/stria terminalis are associated with the remission of PTSD following treatment (Kennis et al., 2015). Further, recent work from our laboratory demonstrates the microstructure of the fornix/stria terminalis varies positively with PTSD symptom severity (Harnett et al., 2018a). Taken together, the present literature suggests the emotional dysfunction associated with PTSD is partially due to changes in the microstructure of the fornix/stria terminalis, which connects the amygdala and hippocampus to the hypothalamus.

2.4. Biochemistry

The biochemistry of the brain is also altered in PTSD patients. Specifically, N-acetyl-aspartate (NAA) and glutamate/glutamine (Glx) concentrations vary within the PFC and hippocampus as a function of PTSD (Karl and Werner, 2010; Rosso et al., 2017; Yang et al., 2015). NAA is related to the relative number and health of neurons within brain tissue, while Glx reflects intra- and extracellular glutamate/glutamine levels (Gujar et al., 2005). These biochemical measures index cellular processes that may make important contributions to the cognitive-affective dysfunction observed in PTSD patients.

PTSD has been linked to alterations in the concentrations of biochemicals within the hippocampus. Several reports have observed reduced NAA concentrations within the hippocampus of PTSD patients (Karl and Werner, 2010; Mahmutyazicioğlu et al., 2005; Rosso et al., 2017). NAA concentrations have been linked to neuronal loss and thus serve as a marker of neuronal health (Gujar et al., 2005). These NAA findings converge with prior research that suggests PTSD is related to the death of neurons within the hippocampus (Karl et al., 2006; Kühn and Gallinat, 2013). Further, recent reports have found increased hippocampal glutamate (Glu) concentrations in PTSD patients compared to non-PTSD controls (Rosso et al., 2017). More specifically, Glu to NAA ratios varied positively with PTSD symptom severity (Rosso et al., 2017). Interestingly, prior work indicates stress exposure potentiates glutamatergic activity within the hippocampus (Lowy et al., 1995). Increased glutamate activity can produce an excitotoxic cellular environment that damages neurons (Choi et al., 1988; Mark et al., 2001). Thus, stress may lead to excitotoxic effects within the hippocampus. Therefore, posttraumatic stress may disrupt glutamatergic regulation in the hippocampus, leading to neuronal death and producing the hippocampal-dependent learning deficits that are often observed in PTSD patients.

In addition to the hippocampus, biochemical concentrations within dorsomedial and ventromedial PFC are also altered in PTSD. Prior PTSD studies have predominately focused on the anterior cingulate cortex (ACC) which is part of the dorsomedial and ventromedial PFC. Several studies have reported reduced NAA concentrations within the ACC of PTSD patients (De Bellis et al., 2000; Ham et al., 2007; Karl and Werner, 2010; Meyerhoff et al., 2014). Interestingly, Glx concentrations within the rostral ACC are reduced in PTSD (Yang et al., 2015). Further, Glx concentrations vary with PTSD symptom expression (Yang et al., 2015). However, these effects appear to differ between the ventromedial PFC and dorsomedial PFC. While PTSD patients show reduced Glx concentrations within the ventromedial PFC (Yang et al., 2015), prospective measures of Glx within the dorsomedial PFC are positively related to future PTSD symptom expression (Harnett et al., 2017b). Together, the current literature suggests PTSD is related to alterations in the biochemistry of the dorsomedial and ventromedial PFC.

Currently, there is limited knowledge on human amygdala NAA and Glx concentrations. NAA and Glx are most commonly assessed using proton magnetic resonance spectroscopy (1H-MRS) and conventional limitations to this technique often preclude collection of amygdala spectra. For example, the amygdala is a small structure within the medial temporal lobe and MR signals from this region are often distorted due to the proximity of sinus cavities. Thus, MRS investigations of the amygdala in PTSD patients have been limited. Prior research using MRS in animals has not observed changes in NAA concentrations within the amygdala of rats following a single prolonged stress procedure (Knox et al., 2010). However, recent work suggests there may be brief, transient changes in NAA concentrations following stress exposure (Han et al., 2015). Further, PTSD research with comorbid bipolar disorder (BPD) patients has not observed differences in NAA between patients with and without comorbid PTSD (Hoerst et al., 2010). Thus, given the conflicting animal literature and the limited human PTSD research, the relationship between posttraumatic stress and amygdala NAA concentrations should be studied further.

Similar to NAA there is little human MRS research on amygdala Glx concentrations in PTSD. However, non-MRS studies have suggested there are alterations of amygdala glutamatergic systems in PTSD patients. Prior animal model work has demonstrated that glutamate antagonists attenuate startle responses (Walker and Davis, 1997), particularly after exposure to a single-prolonged stressor (Khan and Liberzon, 2004). Interestingly, prior positron emission topography research has observed a moderate increase in glutamate receptor availability within the amygdala of PTSD patients relative to controls (Holmes et al., 2017). These findings suggest glutamate activity within the amygdala may be up-regulated in PTSD patients, resulting in exaggerated startle responses. All together, the prior research suggests biochemical variations are important for PTSD, but more research is needed to fully characterize these alterations within the amygdala.

2.5. Summary of prior research

In summary, the current literature suggests PTSD is associated with disruptions in the neurobiology that supports fear learning and memory. These fear learning and memory processes are dependent upon the PFC, hippocampus, and amygdala. Disruption of the function, structure, and biochemistry of these brain regions is associated with PTSD. The impact posttraumatic stress has on emotional function appears to be mediated, in part, by the dysregulation of glutamatergic systems. This glutamatergic dysregulation may then lead to cell death due to excitotoxicity and may play an important role in modifying the structure of brain regions that support fear learning and memory. Neuronal loss within the PFC may underlie the altered white matter microstructure of the cingulum bundle and uncinate fasciculus, disrupting important regulatory processes (e.g., ventromedial PFC inhibition of the amygdala). Specifically, structural changes affecting projections both to and from the ventromedial PFC may lead to diminished ventromedial PFC activation and impair the regulatory functions it

supports. Disruption of these regulatory processes appears to underlie the enhanced fear expression (e.g., greater fear responses and fear overgeneralization) often observed in PTSD patients. Specifically, reduced ventromedial PFC regulatory control may lead to greater communication between the amygdala and the hypothalamus. This increased interaction may lead, in turn, to the strengthening of the structural connection (i.e., fornix/stria terminalis) between the amygdala and hypothalamus, and ultimately enhance the expression of the emotional response. Of note, a similar process may occur in the dissociative subtype of PTSD such that regulatory processes supported by the dorsomedial and ventromedial PFC are altered, although in this case the alterations may result in greater suppression of the emotional response. Unfortunately, there is limited data on the structural and biochemical alterations that are associated with the dissociative subtype of PTSD. Although disruptions in fear-related neural circuitry appear to play an important role, the specific structural and biochemical processes that underlie this specific phenotype remain unclear. Taken together, prior work suggests that functional, structural, and biochemical alterations within the brain regions that support fear learning and memory processes ultimately underlie the emotional dysfunction in PTSD.

3. Neurobiological signatures of PTSD

A key goal of modern translational neuroscience is to develop accurate models of the neurobiology that underlies the development of trauma and stress-related disorders. Although prior work has made substantive contributions to our knowledge of the neural basis of PTSD, there remain several gaps in our current understanding of the brain mechanisms that mediate the development of the disorder. First, prior PTSD research has primarily focused on findings from a single neuroimaging modality (e.g., functional brain imaging). Thus, integrative multimodal neuroimaging studies of PTSD are currently lacking. Without further multimodal neuroimaging research, our ability to construct comprehensive neurobiological models of PTSD will be hampered. Second, limited research has investigated the acute impact of posttraumatic stress on the human brain. In contrast, the chronic effects of posttraumatic stress have received wide-spread attention. The acute effects of posttraumatic stress on brain function, structure, and biochemistry likely play a critical role in the development of trauma and stress-related disorders, ultimately driving the emotional dysfunction observed in PTSD. Thus, investigations into the impact of acute posttraumatic stress may elucidate the etiology of PTSD.

3.1. Multimodal neuroimaging and PTSD

Multimodal neuroimaging can be used to directly assess the relationships between brain function, structure, and biochemistry that underlie trauma and stress-related disorders. Specifically, the use of multiple neuroimaging modalities to assess brain function, structure, and biochemistry within a single study could elucidate the complex, interdependent neural processes that lead to PTSD. Prior PTSD research has primarily focused on unimodal studies of the brain (e.g., brain function alone). However, although reports on different modalities (e.g., function, structure, and biochemistry) can be qualitatively compared, it is difficult to assess multimodal relationships solely through independent reports. Specifically, one cannot directly test relationships between different neurobiological processes through separate unimodal reports. Thus, current unimodal approaches limit the confidence of inferences that can be made about the interdependent neural processes that underlie PTSD. Therefore, multimodal neuroimaging is necessary to develop comprehensive models of PTSD. Multimodal neuroimaging offers researchers several approaches to study the complex neurobiological relationships that are linked to PTSD. One approach is to separately analyze multiple imaging modalities and assess relationships between the data types using traditional analytic techniques (e.g., correlation analysis). For example, prior research has used multimodal neuroimaging to investigate linear relationships between the function and structure of the amygdala within traumatized individuals. These studies provided direct evidence of an inverse relationship between amygdala activity and volume within traumatized individuals (Ganzel et al., 2008), as one might hypothesize based on prior unimodal reports from separate studies. However, brain function, structure, and biochemistry may also covary in ways that are not easily observed by common analytic techniques. Thus, more advanced multimodal analytic approaches may elucidate complex associations that are hidden within neuroimaging data.

Multimodal data fusion approaches are well suited to identify the complex relationships between brain function, structure, and biochemistry in neuroimaging data. These techniques provide a multivariate approach to integrate data from distinct neuroimaging modalities and identify latent neurobiological patterns that may be hidden from traditional analytic approaches (Calhoun and Sui, 2016). A number of data-fusion techniques are currently available and have been applied to neuroimaging data (Calhoun and Sui, 2016; Douaud et al., 2014; Groves et al., 2011). Many of these techniques are data-driven approaches that work to reduce the high-dimensionality of the neuroimaging data to find common components among the data. Further, these techniques are not constrained by a priori assumptions of relationships between data modalities. Thus, these techniques allow for an unbiased integration of neuroimaging data and can reveal important neurobiological characteristics of both healthy and psychiatric populations.

Multimodal fusion approaches have gained increasing popularity in assessing healthy and psychiatric populations. Prior reports using data fusion techniques have investigated the relationship between aging and brain structure (Douaud et al., 2014; Groves et al., 2012). Specifically, integrated analyses of gray and white matter measures from MRI were used to characterize the neural correlates of the aging process. Other work has used multimodal fusion in data from the Human Connectome Project to elucidate the neurobiology of cognitive control in healthy individuals (Lerman-Sinkoff et al., 2017). These techniques have also been applied to patient populations as well. For example, multimodal fusion has been used to characterize differences in brain function-structure relationships between stroke patients and healthy controls (Griffis et al., 2017). Further, prior work has used multimodal fusion to reveal differences in the brain function-structure relationships that are disrupted in bipolar disorder and major depressive disorders (He et al., 2017). Multimodal neuroimaging approaches have also been applied to studies of schizophrenia, and have revealed latent multivariate patterns across brain function, gray matter, and white matter microstructure that distinguish patients from healthy controls (Abrol et al., 2017; Sui et al., 2013). Taken together, prior work demonstrates that multimodal analytic techniques may offer a powerful approach to investigate the neurobiology of psychiatric disorders, and may provide an important tool for future PTSD research.

Multimodal neuroimaging may also help dissociate PTSD-specific neurobiological processes from co-morbid conditions. For example, PTSD and other psychological conditions (e.g., substance use disorder, depression, or anxiety) often co-occur (Brady et al., 2000). These co-morbid conditions may impact neuroimaging measures and make it difficult to determine whether measured neural differences are due to PTSD, the co-morbid condition, or a combination of the two. Multimodal imaging approaches may facilitate the identification of dysfunctional neural processes that are specific to PTSD. For example, prior studies have used a combination of measures of brain function and white matter structure to elucidate differences between PTSD patients with versus without post-concussive syndrome (Rangaprakash et al., 2017). Specifically, concurrent analyses of brain function and white matter data revealed disparate results that provided evidence of neural disruption that differentiated PTSD patients with from those without other psychiatric comorbidities. Additionally, a recent report

successfully fused distinct neuroimaging modalities (i.e., brain activity and gray matter measures) together in PTSD patients (Stout et al., 2018). The report demonstrated that fused data from the supplementary motor area and insula distinguished PTSD patients with mild traumatic brain injury (mTBI) from those without mTBI. Further, individual variability in the fused data varied with the severity of posttraumatic stress and depression symptoms. These findings suggest multimodal neuroimaging may also help to characterize and distinguish neural processes that are specific to PTSD from those of other comorbid conditions. Thus, multimodal neuroimaging may provide an effective method to distinguish specific neurobiological mechanisms of PTSD from potential confounds.

In addition to separating PTSD from comorbid processes, multimodal fusion approaches may also be useful in delineating subtypes of PTSD. As discussed previously, PTSD symptom expression varies considerably from person to person and can occur with or without dissociative symptoms. However, although there are separate subtypes and presentations of PTSD, these distinct subtypes of PTSD may share similar unimodal imaging features. For example, PTSD with and without dissociative symptoms are both associated with reduced hippocampal volume compared to healthy controls (Chalavi et al., 2015a, 2015b). Given that these PTSD subtypes share many similar phenomenological features, it is not surprising that there is considerable overlap in unimodal neuroimgaging findings. Thus, it would likely be difficult to separate these two subtypes of PTSD based on unimodal imaging data alone. In contrast, multimodal approaches may be able to capture neurobiological differences between these PTSD subtypes. For example, a recent study demonstrated that combined assessment of mean amplitude low-frequency fluctuation (i.e., amplitude of spontaneous brain activity) and functional connectivity data during resting-state fMRI was able to separate typical PTSD from its dissociative subtype (Nicholson et al., 2019). However, as noted previously, there has been limited prior research into other neurobiological facets of the dissociative subtype of PTSD (e.g., structure and biochemistry). Thus, further investigations into the neurobiology of heterogeneous presentations of PTSD are needed to more fully leverage multimodal data analyses. However, taken as a whole, multimodal approaches are a promising avenue for developing brain-based markers to differentiate PTSD subtypes.

Despite the benefits of multimodal MRI approaches to the study of PTSD, several challenges still limit its current use. Although many studies acquire multiple types of MRI data, it is both computationally and conceptually expensive to integrate data from these distinct modalities. For example, a unimodal analysis of fMRI data in PTSD can require a myriad of technical (e.g., knowledge of fMRI processing standards) and statistical skills (e.g., first-level and group-level models). The knowledge set to analyze a single modality for a psychiatric patient population may itself be the basis for an entire area of inquiry. The addition of other modalities to the inquiry adds layers of complexity to the analysis and interpretation of the data. This additional complexity comes even before considerations of how to best perform the multimodal MRI fusion analyses. Therefore, the implementation of multimodal analyses to understand the neurobiology of PTSD will require collaborative efforts from research teams with diverse technical expertise to construct accurate, multimodal profiles of the neurobiology of PTSD susceptibility.

3.2. Investigations of recent trauma exposure

Prior PTSD research has primarily focused on patients with chronic PTSD and limited research to date has investigated the acute effects of posttraumatic stress on brain function, structure, and biochemistry. Importantly, the acute posttraumatic stress associated with trauma exposure must play an important role in the neural abnormalities that are observed in those that develop PTSD. Specifically, given that PTSD has a measurable cause (i.e., trauma exposure), it may be the case that there are acute effects that contribute to the development of the disorder. The acute effects of posttraumatic stress should be detectable and may elucidate neural markers of PTSD susceptibility (i.e., an individual's likelihood of developing PTSD). Unfortunately, relatively limited research has utilized neuroimaging to investigate the acute effects of posttraumatic stress (Harnett et al., 2018a, 2018b; Harnett et al., 2017b, 2018b; Stevens et al., 2017; van Rooij et al., 2018). Relatedly, limited research has attempted to characterize the neural changes that develop over time following trauma exposure (Bonne et al., 2001). Thus, significant gaps remain in our understanding of the acute effects of posttraumatic stress on human neurobiology. A thorough understanding of such effects would allow us to construct comprehensive models of PTSD development.

Recent work has begun to identify functional brain signatures of PTSD in the acute phase following trauma exposure. Notably, as is seen in those with chronic PTSD, the neural substrates that support fear learning show acute dysfunction following trauma exposure (Harnett et al., 2018b; Stevens et al., 2017; van Rooij et al., 2018). Recent research suggests Pavlovian fear conditioning processes, in particular safety learning, are disrupted by trauma exposure, which may be due to the dysfunctional disengagement of the dorsomedial PFC during safety cues (Harnett et al., 2018b). Further, ventromedial PFC and amygdala activity to fearful faces acutely following trauma is tied to the future expression of PTSD symptoms (Stevens et al., 2017). Thus, disengagement of prefrontal control mechanisms and enhanced amygdala activity acutely following trauma may partially underlie the development of PTSD. In addition, hippocampal activation related to behavioral inhibition acutely following trauma is also negatively related to future PTSD development (van Rooij et al., 2018). Together, these findings demonstrate that acute dysfunction of neural activity within the fear learning network is a potential vulnerability factor for the future development of PTSD after trauma.

Similarly, structural alterations of the fear learning network may also be a vulnerability factor for PTSD. Prior work has assessed the volume of the hippocampus and amygdala of traumatized individuals within one week and again at six-months post-trauma. Hippocampal and amygdala volumes did not change between the initial and six-month assessments in participants that developed PTSD (Bonne et al., 2001). Further, no differences in hippocampal or amygdala volume were observed at either assessment between PTSD patients and trauma-exposed controls. These findings suggest reductions in hippocampal volume may be due to the chronic effects, as opposed the acute effects, of posttraumatic stress given that other research has demonstrated chronic PTSD is associated with reduced hippocampal volume (Bremner et al., 1995; Gilbertson et al., 2002; Kühn and Gallinat, 2013). Further, the microstructure of the cingulum bundle and uncinate fasciculus have been linked to PTSD symptoms, such that reduced microstructure of these white matter tracts is related to greater PTSD symptom expression (Harnett et al., 2018a). However, fornix/stria terminalis microstructure shows a positive relationship with PTSD symptom expression (Harnett et al., 2018a). Notably, the white matter microstructure of these tracts does not differ between trauma-exposed and non-trauma-exposed participants, suggesting white matter microstructure may be a pre-trauma vulnerability factor. Thus, some structural signatures of PTSD may be pre-trauma vulnerability factors (e.g., white matter) while others may develop over time as a result of the chronic stress of PTSD (e.g., gray matter).

Biochemistry of the brain has also been assessed acutely following trauma exposure. Prior research has demonstrated Glx concentrations within the dorsal ACC of recently trauma exposed participants varies with PTSD symptom expression (Harnett et al., 2017b). Specifically, Glx concentrations measured within one-month of trauma exposure were positively related to PTSD symptoms both at 1 and 3 months post-trauma. Another study found that NAA levels within the ACC were related to PTSD development (Su et al., 2018). Specifically, greater NAA concentrations were found within participants who developed

PTSD compared those that did not. Together, these findings suggest acute alterations in brain biochemistry within the fear network are related to the development of PTSD following trauma.

The acute effects of posttraumatic stress appear to lead to long-term changes in the neural processes that support fear learning and memory, and ultimately lead to the development of PTSD. Therefore, longitudinal research is needed to better understand posttraumatic changes in neurobiology that develop over time. However, limited longitudinal research to date has investigated changes in brain function, structure, and biochemistry that develop over time following trauma exposure (e.g., from acute to chronic stages). The limited research that has investigated changes in human neurobiology over time following trauma has meaningfully advanced our understanding of the development of PTSD. Therefore, further longitudinal investigations of the acute and long-term effects of posttraumatic stress would benefit our understanding of the neurobiology that underlies the development of this disorder.

4. Conclusion

The extant literature provides important information about the neurobiology of PTSD. A PFC-hippocampus-amygdala network appears to mediate fear learning and memory processes that are important for healthy emotional function. Disruption of the function, structure, and biochemistry of this network has been linked to PTSD. Thus, prior work has established the importance of this PFC-hippocampus-amygdala network in PTSD and provides clues as to the mechanisms that underlie development of this disorder. However, future research on the neural basis of PTSD would benefit from multimodal neuroimaging techniques that investigate the acute effects of posttraumatic stress, then follow changes in these measures over time. Multimodal neuroimaging has the potential to reveal hidden patterns among distinct neuroimaging modalities that would greatly enhance our ability to develop comprehensive neurobiological models of PTSD. Further, multimodal neuroimaging would facilitate the identification of neural processes that are specific to PTSD and independent of comorbid factors. Additional investigations into the acute effects of posttraumatic stress are also necessary to understand the mechanisms that underlie the development of PTSD. These research directions would expand our knowledge of the neurobiology of PTSD and pave the way for future translational efforts to develop improved diagnostic markers, early intervention techniques, and targeted treatment approaches for trauma and stress-related disorders.

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