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Context Processing and the Neurobiology of Post-Traumatic Stress Disorder

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Summary

Progress in clinical and affective neuroscience is redefining psychiatric illness as symptomatic expression of cellular/molecular dysfunctions in specific brain circuits. Post-traumatic stress disorder (PTSD) has been an exemplar of this progress, with improved understanding of neurobiological systems subserving fear learning, salience detection, and emotion regulation explaining much of its phenomenology and neurobiology. However, many features remain unexplained and a parsimonious model that more fully accounts for symptoms and the core neurobiology remains elusive. Contextual processing is a key modulatory function of hippocampal-prefrontal-thalamic circuitry, allowing organisms to disambiguate cues and derive situation-specific meaning from the world. We propose that dysregulation within this context-processing circuit is at the core of PTSD pathophysiology, accounting for much of its phenomenology and most of its biological findings. Understanding core mechanisms like this, and their underlying neural circuits, will sharpen diagnostic precision and understanding of risk factors, enhancing our ability to develop preventive and “personalized” interventions.

Introduction

Historical perspective on the evolution of the PTSD concept

The past two decades have witnessed a fundamental transformation in our understanding and conceptualization of psychopathology. Cultural, clinical and scientific perspectives increasingly converge on a view of psychiatric disorders as dysfunction within specific components of the central nervous system, rather than “functional” disorders unrelated to neurobiological substrates. This shift has forced theoretical approaches to grapple with the biological underpinning of psychological processes, grounding our models of illness in growing understanding of neural circuits, cellular mechanisms and molecular processes. This conceptual shift has been challenging but also transformational in the study of post-

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traumatic stress disorder (PTSD), which has seemed like a quintessentially psychological illness because it develops in reaction to specific environmental events.

The deleterious effects of severe trauma on the human psyche have been documented for centuries, generally depicted as “normative” responses to extraordinary circumstances. During the 19th and early 20th century, with emergence of psychiatry and psychology as clinical disciplines, the more debilitating consequences of trauma were re-conceptualized as clinical conditions, amenable to scientific inquiry and treatment (Jones, 2006). Conceptual challenges persisted, however, in sometimes controversial efforts to differentiate true psychopathology from normative responses to extreme circumstances. Resolution of these controversies awaits empirical documentation of causative neurobiological pathways, which will facilitate an understanding of how brain-based vulnerabilities lead to dysregulated psychological responses, and emergence of disorder-specific neurobiological abnormalities. PTSD has been studied intensively in recent decades; but despite important breakthroughs, we still lack a comprehensive, integrated model that coherently and parsimoniously explains both its phenomenology and its neurobiology. In this Perspective, we will describe PTSD as a clinical entity and touch on its well-established neurobiological findings. We will then try to organize emerging findings within existing conceptual frameworks, highlighting the value and limitations of those frameworks. Finally, we will describe a new framework, focused on the neural circuitry of context processing, which adds additional explanatory power and can potentially better integrate more of what we currently know about this important disorder.

PTSD as a clinical phenomenon

In the absence of scientific understanding of the pathophysiologic processes involved in PTSD development, the “gold standard” for defining it has been expert consensus as reflected in DSM criteria. These criteria have changed as clinical perspectives and scientific understanding have evolved, but they have remained phenomenological at their core since they are not yet grounded in biological processes and CNS neuro-circuitry. Despite periodic and sometimes substantial changes, there has been consistent agreement on three sets of symptom clusters considered characteristic of PTSD -- the intrusive, avoidant and hyperarousal clusters. These encompass unwanted and repeatedly re-experienced memories, sensations or dreams associated with the trauma (intrusive cluster); behavioral avoidance of trauma reminders; and excessive physiological arousal both in response to trauma cues or independently (e.g., sleep problems). These core clusters have been embraced in DSM III, IV, and 5, but other symptoms or criteria have been added (negative affect or reckless behavior in DSM-5), deleted (trauma outside of usual human experience), or included descriptively (shame/guilt, dissociation). Shifting criteria create scientific challenges to sample homogeneity across time and undermine clinical efficacy when targets for intervention are imprecise and continuously moving. As clinician-scientists, we will do better when we can target precisely defined dysregulations within specific neural circuits sub-serving particular, mechanistically relevant brain functions. As we identify underlying mechanisms rooted in specific neural circuits, diagnostic precision will sharpen and our ability to “personalize” interventions will be enhanced. For PTSD, we will also be able to go beyond treatment and apply preventive interventions before or immediately after trauma exposure.

PTSD pathophysiology -- early studies

Prior to development of *in vivo* functional neuroimaging and valid animal models, allowing direct examination of CNS structure and function, biological study of PTSD focused on identification of abnormal peripheral markers. The best replicated of these have been psychophysiological indices of autonomic nervous system (ANS) function, and altered blood, saliva and urine concentration of stress hormones and catecholamines. Noradrenergic hyper-reactivity was the most reliably replicated finding in PTSD (Pitman et al., 2012), along with altered function of the hypothalamic-pituitary adrenal (HPA) axis, where hypersensitivity of glucocorticoid receptors was accompanied by unaltered or decreased levels of circulating cortisol (Yehuda, 2001).

ANS abnormalities have been seen at rest and in reaction to trauma cue exposure (Agorastos et al., 2013; Cohen et al., 2000; Lee and Theus, 2012; Minassian et al., 2014; Shah et al., 2013) (for meta-analysis see Pole, 2007). Heart rate variability (HRV) is a sensitive index of ANS function (Bilchick and Berger, 2006; Malik and Camm, 1995) and reductions in it -- which suggest arousal dysregulation and autonomic inflexibility due to sympathetic overdrive and/or parasympathetic insufficiency (Shah et al., 2013; Cohen et al., 2000) -- predict PTSD development whether measured prior to (Minassian et al., 2015) or immediately after trauma exposure (Shaikh al arab et al., 2012). PTSD is also associated with exaggerated catecholamine responses to trauma cues (Liberzon, Abelson, et al., 1999), and elevated levels of NE secretion in 24-hour urine collections (Wingenfeld et al., 2015). PTSD may thus reflect a “hyper-adrenergic state” (Krystal and Neumeister, 2009). Dysregulation is also evident in HPA axis function, but this appears more complex. The more consistent abnormalities involve enhanced dexamethasone suppression of cortisol (Yehuda et al., 1993), often attributed to glucocorticoid (GC) receptor hyper-sensitivity (Yehuda, 2001). This is supported by in vivo assay evidence of GC receptor hyper-sensitivity on lymphocytes (Yehuda, Boisoneau, et al., 1995). Measurement of cortisol levels in PTSD has generally suggested normal (Baker et al., 1999) or reduced levels (Yehuda et al., 1990; Yehuda, Kahana, et al., 1995; Yehuda et al., 1996), though there are some inconsistent reports (Meewisse et al., 2007; Lindley et al., 2004; Pitman and Orr, 1990). Reduced levels would be consistent with GC receptor hypersensitivity and early HPA axis “shutdown.”

Additional peripheral biological abnormalities linked to PTSD require replication, but are consistent with the changes reported above. These include alterations in serotonin systems (Southwick et al., 1999), DHEA (Yehuda et al., 2006), neuropeptide Y (Rasmusson et al., 2000), neurosteroids (Morris et al., 2012), endocannabinoids (Wilker et al., 2016) and endogenous opioids (van der Kolk et al., 1989). Genetic work is rapidly expanding, and has identified PTSD-linked polymorphisms in genes encoding elements within the HPA axis (FKBP5 (Binder et al., 2008) and CRHR1 (Amstadter et al., 2011; White et al., 2013; Etkin et al., 2015)), and the sympatho-adrenal system (ADRB2 (Liberzon et al., 2014) and COMT (Boscarino et al., 2011)). These require confirmation in large-scale GWAS studies, but are consistent with the peripheral findings and suggest that PTSD is characterized by ANS hypersensitivity, associated with or leading to hyperadrenergic states, and a hypersensitive glucocorticoid receptor system. However, potential linkages between these abnormalities and the central mechanisms that drive them remain unknown.

PTSD Neurocircuits

The development of in vivo neuroimaging methodologies and emergence of affective neuroscience have shifted the focus of contemporary neuropsychiatric inquiry to specific neural circuits that might govern the development of PTSD. Converging evidence from human imaging studies and animal models of complex behaviors like fear associated learning has generated powerful, neurocircuitry-based models of its pathophysiology. In the following sections, we selectively review the evolving picture, organizing it within dominant emergent models, identified as (1) an abnormal fear learning model (FL), which encompasses altered fear conditioning, fear extinction and fear generalization hypotheses; (2) an exaggerated threat detection model (TD) which postulates altered attention, anticipation, or "alarm" functions; and (3) a diminished emotional regulation/executive function (EF) model which postulates deficient regulatory capacity of cognitive/executive function regions over emotion generating limbic structures. These models are distinct in their focus on different aspects of PTSD psychopathology and different brain circuits, and may be driven by different cellular and molecular processes. However, they are not necessarily mutually exclusive. Each may explain different aspects of the disorder and a different subset of its biological abnormalities. We then identify important aspects of PTSD that are not explained by these models. Together they can explain much, but they invoke at least three independent pathophysiological processes while leaving some key symptoms and findings unexplained. This is not very parsimonious or conceptually satisfying. It is possible, or even likely, that PTSD is not a single homogeneous disorder but rather is a syndrome that "houses" within it a number of sub-categories with somewhat different presentations, endophenotypes, and pathophysiological mechanisms. Nevertheless the fact that important parts remain unexplained suggests a need for additional, alternative, or more mechanistically expansive models, which might parsimoniously explain both the complex symptomatology of PTSD and its existing neurobiological findings. Following discussion of the FL, TD and ER/EF models, we present a novel model that is both more general and more parsimonious, explaining multiple, not previously explained symptoms, and integrating neurobiological findings within the framework of a focal pathophysiologic process – altered contextual processing (CP). The CP model focuses our attention on dysfunction within specific brain circuits governing the critical adaptive function of contextualization – involving hippocampus (Hpc) prefrontal cortex (PFC), thalamic circuits that modulate activity in amygdala and other limbic and cortical regions. Prior work has identified clear abnormalities in PTSD in the Hpc, PFC, and amygdala, and we suggest that dysfunction within this circuit may be a key pathophysiologic process underlying expression of various PTSD symptoms, in a way that may be able to integrate the contributions of the altered noradrenergic and glucocorticoid functions that have been so consistently documented in this disorder.

Models of Pathophysiology

Abnormal Fear Learning

Learning what is threatening and what is safe is a critical, highly conserved function that had been extensively studied neurobiologically using fear associated learning paradigms and fear conditioning, fear extinction, and fear renewal, processes. PTSD has been conceptualized as heightened fear reactivity that develops in response to exposure to a threatening event, thus

abnormal fear learning was a logical initial place to look in searching for its neurobiology. Fear and safety learning studies have focused mechanistically on a key structure governing these processes – the amygdala – and the complex interplay within the amygdaloid complex (Figure 1) between various nuclei and cell types. Additional processes clearly participate in fear/safety learning, like memory consolidation, fear generalization, and extinction retention, and these involve additional brain mechanisms and regions (e.g., sensory cortex, thalamus, hippocampus, vmPFC). However, within the fear-associated learning framework, these processes and regions have been seen through the prism of their impact on amygdala function and output, rather than as key psychological/pathophysiologic processes shaping PTSD development. Other conceptual models (Threat Detection, Emotional Regulation and Contextual Processing) focus on these extra-amygdala processes as key contributors to PTSD pathophysiology, and they are discussed in subsequent sections.

Fear conditioning/acquisition—The basic circuits of fear conditioning/extinction have been well-worked out. They involve perceptual inputs to thalamus, then to amygdala and to effector systems (LeDoux et al., 1990). Within the amygdala, the basolateral complex (BLC), composed of the lateral (LA), basolateral (BLA), and accessory basal (AB) nuclei, provides the main input to the central nucleus (CE), which constitutes the “final relay” in coordinated outputs to physiological and behavioral effector systems that “express fear” (e.g., Campeau and Davis, 1995). The BLC is the region where associative fear learning, extinction learning, consolidation, and expression are thought to take place (Davis et al., 1994; Fanselow and LeDoux, 1999; Davis, 1992). The cellular substrates for associative learning are long-term potentiation (LTP) and long-term depression (LTD) (Eichenbaum, 1996; Matynia et al., 2002), whereby associative LTP at BLC principal neurons (Blair et al., 2001; Goosens and Maren, 2002) creates a neural link between an unconditioned stimulus (US) and a conditioned stimulus (CS). The phenomenology of PTSD readily suggests disruption in this process, since so many “CSs” (e.g., a backfiring car) seem to be inappropriately linked to the sense of threat carried by traumatic memories. However, BLC sub-networks also have specific connections with prefrontal cortical regions that modulate fear expression, including prelimbic and infralimbic areas. Specific BLC neurons can activate prelimbic PFC during fear learning, while others target infralimbic PFC during extinction (Senn et al., 2014). The BLC can thus provide higher level processors with “information” about what is dangerous and what is safe, potentially for use in future situations that are ambiguous but carry threat potential.

Though intuitively appealing, evidence that PTSD is a disorder of fear conditioning itself is sparse. Trauma exposure itself is readily thought of as an explicit conditioning episode (Elzinga and Bremner, 2002; Jovanovic and Ressler, 2010; VanElzakker et al., 2014), but evidence for abnormalities in fear acquisition in PTSD is conflicting. In typical differential fear conditioning paradigms, where subjects are presented with a US-predicting CS (CS+) and a non-US-predicting CS (CS−), which acts as a safety signal (Lissek et al., 2005), PTSD patients have difficulty differentiating safety from threat (Grillon et al., 1998; Grillon, 2002), but they generally do not show abnormal acquisition of the conditioned response (to CS+) itself (Garfinkel et al., 2014; Milad et al., 2009). Enhanced fear potentiated startle or skin conductance responses have been reported during fear learning by some (Morgan et al.,

1995; Orr et al., 2000; Peri et al., 2000), but not others (Blechert et al., 2007; Milad et al., 2008; Milad et al., 2009). Trauma that can cause PTSD is much more severe than the simple US "threats" used in laboratory studies, but these studies do suggest that the basic ability to acquire new fear conditioned responses is not inherently abnormal in PTSD.

Fear Extinction—Alternatively, it has been proposed that fear associative learning deficits in PTSD stem from abnormalities in extinction or safety learning rather than fear conditioning. A key feature of PTSD is inability to learn that cues once associated with trauma are no longer dangerous -- a process akin to fear extinction in animal models. Dysregulation of extinction, undermining ability to learn that something once dangerous is now safe, may contribute to safety learning deficits in PTSD (Jovanovic et al., 2012). In general, extinction is less robust than conditioning and does not erase an established fear memory. Rather, it creates a safety memory trace that "overlays" the fear memory trace. It is context specific, decays with time, and involves learned inhibition of fear expression. It is mediated by distinct and dedicated pathways within BLC (Jasnow et al., 2013). Dysregulation in the topographically organized BLC output systems may induce imbalances within the larger fear-on and extinction circuits, leading to extinction deficits and persistence of fear memories. Indeed, a number of fear extinction studies report heightened autonomic reactions during extinction learning in PTSD, including increased skin conductance and heart rate and sustained fear-potentiated startle (Orr et al., 2000; Peri et al., 2000; Blechert et al., 2007; Norrholm et al., 2011).

Problems with safety signal learning and inability to modulate fear responses with safety cues (Jovanovic et al., 2009; Jovanovic et al., 2012) also suggest impairment in inhibition of fear pathways. However, other work suggests intact extinction learning in PTSD, but impaired recall of fear extinction memories 24 hours later (Garfinkel et al., 2014; Milad et al., 2009). Intact extinction recall, however, requires cortical inputs from vmPFC to amygdala (Quirk and Mueller, 2008), and intact safety learning after fear conditioning involves inputs from vmPFC and hippocampus (Corcoran and Quirk, 2007). Prefrontal regions have well-traced inputs to the amygdala through which they can amplify (prelimibic) or inhibit (infralimbic) fear expression (Sierra-Mercado et al., 2011). The human homologue of IL (vmPFC) is linked to extinction recall and is smaller in volume and hypo-responsive in PTSD patients (Bremner et al., 2008). Reduced activation of this area is associated with impaired fear inhibition (Jovanovic et al., 2012), raising the possibility that core pathophysiologic processes contributing to deficits in extinction retention may be located in regions outside amygdala and involve neuro-behavioral functions beyond basic fear associated learning processes.

Fear generalization—Fear generalization is another aspect of fear learning implicated in PTSD. Fear generalization occurs when, following conditioning, stimuli other than the CS, but which share some similarities with CS, elicit a fear-related response. This is an adaptive process that facilitates protective responses to situations that are similar to but not identical with situations previously learned to be dangerous (Shepard, 1987). Disruption in generalization (e.g., over-generalization) could contribute to excessive fear expression in PTSD (Lissek and van Meurs, 2015). Generalization is demonstrated by stimulus "response

gradients" -- if during fear conditioning, the CS+ and CS− are chosen to represent two ends along a continuum, fear responses occur to the CS+ and to stimuli close to it on the continuum, with a declining response gradient as the cues approach the CS- end (Lissek et al., 2008). Importantly, the intensity of the US impacts the breadth of generalization beyond the CS+ (Baldi et al., 2004; Ghosh and Chattarji, 2015). A very strong US produces broad generalization. During PTSD-generative traumatic exposure the US (e.g., threat to life) may be sufficient to lead to broad generalization, undermining discrimination between dangerous and safe cues, contributing to high reactivity to "reminders" that bear any resemblance to trauma cues.

Neurobiological studies of generalization in fear conditioning paradigms have been sparse (Likhtik and Paz, 2015). Typical fear conditioning work uses easily discriminable stimuli to ensure strong CS+ vs. CS− differentiation, avoiding potential for generalization (Genud-Gabai et al., 2013). Generalization studies demonstrate neuronally instantiated "tuning curves" that differentiate tones of differing frequencies within auditory cortex, auditory thalamus, and amygdala (Bordi and LeDoux, 1994; Resnik and Paz, 2015; Bordi and LeDoux, 1992). Multiple amygdalar regions are involved, including CE (Ciocchi et al., 2010), other subnuclei (Shaban et al., 2006), and LA (Ghosh and Chattarji, 2015). The amygdala appears to play a role in generating graded generalization curves (Schechtman et al., 2010; Resnik et al., 2011; Laufer and Paz, 2012), and amygdala neurons show tuning properties that could account for behavioral generalization (Resnik and Paz, 2015), perhaps contributing to the broad fear generalization gradients suggested for PTSD. However, amygdala changes in these studies could be due to inputs coming from other brain regions. For example, there is conflicting evidence about the role of auditory cortex in stimulus discrimination and in overgeneralization (Aizenberg and Geffen, 2013; Letzkus et al., 2011). Complex interconnections make it difficult to isolate specific behavioral dysfunction, like overgeneralization, to disruptions at highly specific locations, and the complete circuit that mediates generalization of more complex real-life stimuli might involve interactions between microcircuits within the amygdala (Duvarci and Pare, 2014), the prefrontal-cortex (Likhtik et al., 2014; Klavir et al., 2013; Chavez et al., 2009; Dunsmoor et al., 2011; Courtin et al., 2014), hippocampus (Xu and Sudhof, 2013; Bergado-Acosta et al., 2008; Kaouane et al., 2012), and other regions.

Neuroimaging work has begun to examine the human neurocircuitry of fear generalization, revealing that activity in the amygdala and insula correlate selectively with generalized SCRs, and that functional connectivity between the amygdala and extra-striate visual cortex was selectively enhanced for a perceptually similar cue of high emotional intensity that was never paired with US (Dunsmoor et al., 2011). This suggests that amygdala-cortical communication might be active during generalization. Lissek et al. (2013) reported that gradients of fMRI activity are present in insula and dmPFC, with activity levels declining as similarity to CS+ declined, with a reverse gradient in vmPFC and hippocampus, where activity is greatest to the safety cue. Clinically, some evidence shows that PTSD patients show a failure to discriminate CS+ (threat) from CS− (safety), perhaps due to overgeneralization (Lissek et al., 2005; Jovanovic et al., 2012). However, there is very little experimental evidence specifically demonstrating overly broad generalization gradients in PTSD (Lissek and van Meurs, 2015). It is often assumed that patients with PTSD would

exhibit broad generalization gradients based on their symptom profiles, but empirical documentation is still needed to substantiate this model.

Exaggerated Threat Detection (TD)

Disruptions in Fear/Safety learning or fear generalization can increase reactivity to potentially threatening stimuli. However, threat hyper-reactivity can also stem from processes independent of fear learning. One alternative potential source is in threat detection systems. An ability to detect "salience" in the environment, whether in the realm of threat or reward, is essential for survival, which requires a rapid detection system that can focus attention on salient cues, recruit multiple homeostatic systems to respond to them, and trigger automatic motor routines (Phelps and LeDoux, 2005). Hypersensitive salience detection could heighten vigilance and threat reactivity in PTSD, and activate fear and protective responses disproportionate to actual threats. Exaggerated threat detection has in fact been implicated in PTSD pathophysiology by some investigators (for review, see Shin and Liberzon, 2010; Sripada et al., 2012).

Functional neuroimaging and resting state studies have identified an interconnected network of brain regions, including amygdala, dorsal anterior cingulate cortex (dACC) and insula/operculum (Seeley et al., 2007) that activate when salience is detected in the environment (Figure 2). The amygdala's role in threat detection and fear expression (Ohman, 2005) is well established (see above), but human fMRI work has also demonstrated amygdala reactivity to positive, rewarding or social stimuli (e.g., human faces; Javanbakht et al., 2015). Similarly, dACC is implicated in error and conflict detection, and in autonomic arousal (Critchley, 2004); and anterior insula/operculum activity is associated with anticipation of meaningful events (Simmons et al., 2004), monitoring of internal states (Craig, 2009), and pain perception (Craig, 2003). Functional connectivity between regions of this network creates a circuit, identified as a Salience Network (SN), which activates in response to emotionally arousing information (Seeley et al., 2007). Hyper-reactivity in the nodes of this network, or enhanced connectivity between these nodes, could contribute to hypervigilance, exaggerated threat detection, exaggerated physiological reactivity and other core symptoms of PTSD.

Enhanced threat sensitivity expressed as hypervigilance is indeed a fundamental feature of PTSD. PTSD patients are biased to attend to threat (Buckley et al., 2000), at both supraliminal (Bryant and Harvey, 1995) and subliminal (Harvey et al., 1996) levels. Insula appears to be hyperactive in PTSD during anticipation (Lanius et al., 2007; R. J. L. Lindauer et al., 2008; Aupperle et al., 2012); and increased activation by threat cues is seen in the amygdala (Liberzon, Taylor, et al., 1999; Shin et al., 2004; Bryant et al., 2008). There is evidence that the SN might be hypersensitive to threat in PTSD patients even before trauma exposure, and this sensitivity can predict subsequent symptom development (Admon et al., 2009). Increased dACC reactivity is also seen in PTSD in response to conditioned fear cues (Rougemont-Bucking et al., 2011), demonstrating heightened sensitivity in all of the main nodes of the salience network. Excessive activity in all three nodes (dACC, insula and amygdala) predicted poor response to treatment (van Rooij et al., 2016), suggesting that enhanced SN activity might be involved in symptom persistence. Resting state connectivity

studies have also demonstrated hyper-connectivity within SN regions, involving amygdala, insula, and ACC (Sripada et al., 2012). Such connectivity could enhance processing of threat cues. There thus may be sensitivities at multiple levels within the SN that could contribute to enhanced fear behaviors.

On the cellular/molecular level there is little information on specific processes supporting exaggerated Salience or Threat Detection. Neuronal sensitization within the amygdala to repeated cue exposure is one potential pathway to amygdala hyper-reactivity (Sandi and Richter-Levin, 2009; Li et al., 2010), but this has not yet been directly linked to enhanced Threat Detection or altered SN activity. A key challenge is the lack of animal models of SN hyperactivity, with amygdala reactivity models primarily focusing on conditioning and extinction processes. Another potential pathway to enhanced threat detection in PTSD patients could involve their peripheral ANS abnormalities. For example, low heart rate variability, which may reflect sympathetic-parasympathetic imbalance, is associated with increased threat detection (Melzig et al., 2009; Sevenster et al., 2015) and with risk for development of PTSD (Minassian et al., 2015). Abnormalities in adrenergic tone or glucocorticoids could also contribute to enhanced Threat Detection, as noradrenergic hyperactivity is linked to increased amygdala reactivity (Neumeister et al., 2006) and glucocorticoid receptors, which are abundant in amygdala, have been linked to enhanced anxiety and fear (Schulkin et al., 2005), but direct evidence for a mechanistic pathway through these systems to enhanced threat detection in PTSD is still missing.

Diminished Executive Function and Emotion Regulation

An additional mechanism that could contribute to PTSD pathophysiology involves regulatory processes that modulate responses to emotionally evocative stimuli like threat. Successful navigation in daily life, including avoidance of danger, requires holding information in mind, resisting distractors, switching between tasks, and planning -- tasks that are considered components of Executive Function (EF). EF is a family of capacities by which we manage cognitive processes, and includes mechanisms of working memory, attention, inhibition, and task shifting. Deficits in multiple EF domains are seen in psychiatric disorders and associated with poor social and occupational functioning (Chen and Etkin, 2013). The same mechanisms, and their neural substrates, are also involved in regulation of emotions (ER), in that these cognitive resources are used to modulate emotionally driven behavior. There are multiple aspects of PTSD that could stem from deficits in EF/ER, including memory deficits, exaggerated emotional responses to salient cues, irritability and impulsivity.

Neural activity in dorsal cortical networks, like fronto-parietal attentional networks, has been linked to EF (Niendam et al., 2012). EF participates in shifting neural engagement from a default mode network (DMN), involved in internally-oriented self-directed mentation, to salience and task networks. Imbalance and discoordination between DMN and task networks may contribute to lapses in attention and decrements in performance (Anticevic et al., 2012), as well as to psychiatric disorders (Sheline et al., 2009; Chen and Etkin, 2013; Bartova et al., 2015). ER involves some of the same cognitive control systems, such as memory and attention (Ochsner et al., 2002; Ochsner et al., 2012), supporting the notion of a common set

of prefrontal regions are implicated in the regulation of affective and non-affective responses (Figure 3). For example, the lPFC and mPFC regions activated by emotional regulation (Ochsner et al., 2002) overlap with those activated in working memory and response selection tasks (Miller and Cohen, 2001; Smith and Jonides, 1999; Buhle et al., 2014; Kohn et al., 2014). The most commonly studied type of emotion regulation is reappraisal, which involves conscious, volitional efforts to modulate emotional responses by imposing a “less emotional” cognitive frame on them. In concert with notion of common EF/ER mechanisms, reappraisal activates overlapping regions including dlPFC, vlPFC, dmPFC, dACC, lateral orbitofrontal cortex (OFC), and the posterior parietal lobe (Buhle et al., 2014; Phan et al., 2005).

There is considerable face validity to the idea that deficits in cognitive control and associated top-down inhibitory modulation of autonomic and emotional activation areas might play a role in PTSD. Deficits in EF and/or ER may contribute to functional impairment following trauma and underlie some manifestations of PTSD, including biased attention to trauma cues, heightened emotionality, deficits in memory processes, irritability and impulsivity (Powers et al., 2015). There is in fact growing evidence of dysfunction within EF/ER circuits in PTSD patients. For example, EF-related networks show impaired within-network connectivity in dorsal attention frontoparietal regions in PTSD (Huemer et al., Network architectural and gene expression mechanisms of cognitive dysfunction: insights from post-traumatic stress disorder; under review) and others have reported altered connectivity within and between EF networks in PTSD (Sripada et al., 2012; Chen and Etkin, 2013; Du et al., 2015; Dunkley et al., 2015; Kaiser et al., 2015; Zhang et al., 2015). However, few PTSD studies have examined volitional ER. Only two imaging studies examined cognitive reappraisal in PTSD, with evidence suggesting generally reduced lateral and medial prefrontal activation during reappraisal (Rabinak et al., 2014; New et al., 2009). Reappraisal-related changes were also examined before and after PTSD treatment, with evidence that treatment with selective serotonin inhibitors can ameliorate initial deficits in ER prefrontal brain function, and pretreatment ER-region deficits negatively predict treatment-related gains (MacNamara et al., 2016).

The cellular/molecular mechanisms involved in deficient ER/EF are unknown, largely due to the fact that valid animal models of volitional (and involuntary) emotional regulation are yet to be developed. Noradrenergic hyper-reactivity, postulated to be characteristic of PTSD, has been linked to diminished frontal lobe-mediated executive capacities (e.g., working memory; Arnsten, 2009), and could contribute to diminished EF. Changes in ANS have been associated with reduced performance in a number of EF tasks (e.g., working memory, attention) (Thayer et al., 2009). Whether the peripheral changes “drive” these deficits in CNS function or are downstream effects that feed back is not known. In either case, they could be contributing to EF abnormalities in PTSD. However, while ER deficits are intuitively appealing and somewhat promising based on pilot data, direct evidence for them as contributing factors to PTSD pathophysiology, using established ER paradigms, remains sparse.

Explanatory Gaps and Remaining Questions

The Fear Learning/Generalization, Threat Detection and Emotional Regulation models can account for many of the signs and symptoms of PTSD. *Abnormal Fear Learning and generalization* readily account for key features like the dominance of fear over safety memories, generalization of fear responses to any "trauma-related" stimuli, exaggerated psychophysiologic and adrenergic reactivity, and hypervigilance. Insofar as avoidance of trauma reminders represents a "defensive" strategy to prevent recurrence of these strong fear responses, avoidance symptoms could be explained as bi-products of altered fear learning. The *Abnormal Fear Learning model,* however, does not offer satisfying explanations for other key PTSD features such as spontaneous (non cue-triggered) intrusions, nightmares and other sleep disturbances, emotional numbing or pervasive negative affect, or the behavioral recklessness often seen in PTSD, leading to re-traumatization. Emotional numbing and re-exposure to traumatic environments are in fact particularly difficult to reconcile with a view of PTSD as a disorder of exaggerated fear and diminished safety learning.

Exaggerated Threat Detection and *Diminished EF/ER* models, on the other hand, offer plausible explanation for the presence of threat-focused attentional bias, working memory deficits and hyperarousal in PTSD, which could lead to hypervigilance, and exaggerated emotional and physiologic responses. Exaggerated emotional responses and failure to regulate emotions could contribute to pervasive anger and impulsivity. They could also generate avoidance behavior and contribute to the emergence of intrusive memories in response to traumatic reminder cues. These models, however, have difficulty explaining the pervasiveness of trauma memories and, like the FL model, can not explain spontaneous recollections and intrusions, sleep abnormalities, emotional numbing or re-traumatization.

The main PTSD symptoms left unexplained by these three models are spontaneous (non-cued) recollections, nightmares and other sleep abnormalities, emotional numbing and reckless behavior leading to re-traumatization. Neurobiologically, they can account for exaggerated psychophysiologic reactivity and a hyperadrenergic state, triggered by trauma or trauma-like cues. However, they cannot readily integrate other neurobiologic abnormalties, such as structural hippocampal deficits, HPA axis dysregulation, genetic risk factors like FKBP5 or ADRB2, and altered sleep physiology. These models also require a number of independent pathophysiologic processes in several areas of the CNS to explain as much as they can explain, while leaving important symptoms and findings unexplained. Furthermore, as described above, existing empirical evidence in support of the proposed mechanisms is limited in some places and often contradictory. PTSD could actually be a collection of somewhat distinct neurobiological entities. If so, the FL, TD and EF models might correspond to specific disorder subtypes. However, given the empirical gaps noted and important phenomenological and neurobiological features still unexplained, ongoing pursuit of a more general and parsimonious explanation of PTSD's pathophysiology is clearly still warranted.

A New Model: Deficient Context Processing

In search of a more comprehensive and parsimonious explanation of the full range of PTSD symptoms and the disorder's neurobiology, we have hypothesized a core pathophysiological

deficit within neural circuits that process the contextual information that is used to modulate emotional responses (Liberzon and Sripada, 2008; Maren et al., 2013). This model is firmly rooted in prior work but it expands upon previous models, by reframing them through the lens of context processing, in an effort to better integrate existing understanding and evidence with the "missing pieces" that remain unexplained.

Functionally, the concept of context has been used to refer to general cognitive, semantic or 'emotional' backgrounds that allow one to derive situation-informed meaning from the world (Maren et al., 2013). Contexts are composed of many stimulus elements that are assembled into configural, or 'contextual', representations, perceived as a *"gestalt"* and acquired rapidly (Maren et al., 2013). Salient cues may require radically different responses in different situations – the critical function of context processing is to match cued responses to the "needs" of a given situation or context (Maren et al., 2013). For example, spotting a mountain lion in one's back yard is life threatening, but in a zoo it is exciting (even though the safety features can be well hidden). Contextual information allows us to freeze, flee, or enjoy the view of the lion, depending on the situation. Considering the central role of context in the flexible representation and retrieval of information and in resolving ambiguity, contextual processing deficits would lead to cue-focused behavioral reactivity, which is less flexible and more likely to be situationally inappropriate, potentially contributing to a broad range of PTSD symptoms.

The neural circuits involved in context processing have been extensively studied, largely through studies of associative learning (Bouton, 1993, 1994), building foundation for CP models of psychopathology by revealing the fundamental mechanisms whereby contexts are encoded and how they modulate memory retrieval (Corcoran and Maren, 2001). These studies have shown that the hippocampus plays a critical role in contextual learning and memory (Holland and Bouton, 1999), which is consistent with its role in episodic memory and spatial representation. Unique contextual representations are established in the hippocampus by population coding of spatial properties of the environment, integrating them with non-spatial information (e.g., time, prior experience, internal states) into a gestalt that becomes context (Hayman et al., 2003). Converging findings from animal and human studies (Alvarez et al., 2008; Marschner et al., 2008) indicate that the role of the hippocampus is critical, although not exclusive, in context encoding, and that hippocampal and prefrontal cortical regions interact in context retrieval (Figure 4). The hippocampus establishes new memory representations, minimizing overlap with previous memories, but it also helps to retrieve old memory based on partial information. These processes are known as pattern separation and pattern completion, respectively (see Yassa and Stark, 2011 for review). The ability to differentiate the zoo's diorama from a real mountain landscape, even though the former was designed to invoke the latter, depends upon this process of pattern separation, helping to differentiate safety from threat. In contrast, pattern completion processes allow one to retrieve memory based on partial or incomplete information, for example, allowing one to take quick, protective action with just a glimpse of a "lion-like" silhouette in the backyard. These processes have clear relevance to PTSD, where a bias towards pattern completion in the face of a partial threat cue, and difficulty "reading" the contextual nuances needed for pattern separation, would make it difficult to discriminate threat from safety and would foster threat generalization (Kheirbek and Hen, 2014; Kheirbek et al., 2012),

contributing to hypervigilance and hyperarousal. Impairment in hippocampal subregions involved in pattern separation (i.e., the dentate gyrus) could result in recurrent retrieval of trauma memories in response to partial cues, leading to generalized fear responses that are incongruous with the current context.

The mPFC is another critical component of context processing circuitry. It is highly interconnected with hippocampus, and bidirectional interactions between hippocampus and mPFC have been implicated in contextual memory and in PTSD (Jin and Maren, 2015). Ensembles of mPFC neurons track environmental contexts (Hyman et al., 2012) and integrate contextual recognition and the context-US association during fear associated learning (Zelikowsky et al., 2014). Lesions in mPFC disrupt remote context memory (Quinn et al., 2008), suggesting that mPFC helps maintain context representations over time, since the role of the hippocampus in this function appears to be time-limited (see Sutherland and Lehmann, 2011). While ventral hippocampus is thought to encode non-spatial contextual information such as odors, bodily states, and emotions (Pennartz et al., 2011), mPFC creates associations between events, contexts, locations, and emotional responses (Euston et al., 2012). Preston & Eichenbaum (2013) suggest that while hippocampus forms novel memories, the prefrontal cortex "…accumulates features of related memories that compose the 'context' of a set of connected experiences" (p. 766). In this role, mPFC both guides appropriate memory retrieval by using the context to resolve conflicting information, and participates in memory formation by resolving conflicts between pre-existing schemas and new events. This process of organizing multiple features into a single, coherent representation, integrating temporal and spatial information, involves theta-oscillations that functionally bind hippocampus and PFC (Herweg et al., 2016). If this system is not working well, (being a bit "unmoored" in time and space) it could create vulnerability to over-react to potential indicators of threat, enhancing vigilance, providing face validity for potential relevance to PTSD.

Indeed, evidence is accumulating that dysfunction within this interconnected context processing circuitry -- which involves hippocampus, prefrontal cortex, thalamus, and amygdala -- may play a central role in the pathophysiology of PTSD. With direct relevance to fear and safety learning, human studies have confirmed the engagement of mPFC regions (including subgenual ACC, vmPFC and OFC) (Gottfried and Dolan, 2004; Phelps et al., 2004; Lang et al., 2009), dACC, rostral mPFC (LaBar et al., 1998; Veit et al., 2002; Gottfried and Dolan, 2004; Knight et al., 2004; Phelps et al., 2004; Milad et al., 2007; Lang et al., 2009), and hippocampus (Knight et al., 2004) in extinction of fear memory, a process that is inherently context dependent. At the same time, diminished mPFC signal had been repeatedly demonstrated in PTSD and diminished vmPFC signal is linked to PTSD deficits in extinction recall/retention (Shin and Liberzon, 2010; Etkin and Wager, 2007). In concert, abnormalities in processing of contextual information can lead to cue-elicited fear responses, in association with hypo-activation in vmPFC and hyper-activation of dACC (Rougemont-Bucking et al., 2011). Diminished vmPFC activation is also seen during a Go/NoGo "inhibitory" task in PTSD subjects, and linked to enhanced fear-potentiated startle responses during safety signal learning (Jovanovic et al., 2013). *Together, this emerging evidence suggested to us that abnormalities seen in PTSD in retention of extinction or in fear renewal, or failure to learn or recall safety cues, could all stem from a general deficit in contextual*

processing, rooted in a hippocampal-prefrontal-thalamic circuitry dysfunction. As an initial test of this hypothesis, we extended a standard conditioning/extinction paradigm into a renewal phase, making the counter-intuitive prediction that PTSD patients would fail to detect "danger" signals, despite their continuous hypervigilance for threat, if those signals were contextual in nature. We hypothesized that extinction recall deficits and fear renewal deficits would both be present due to disrupted hippocampal functioning, since both extinction recall and fear renewal are context- and hippocampal-dependent processes. If PTSD patients indeed exhibit such a general deficit, then when presented again with the original conditioning context in a renewal test, they would "fail" to display an appropriate return of the conditioned fear response, similar to their reported inability to recall extinction when exposed to the extinction context. This is exactly what happened (Figure 5, bottom panel). PTSD patients failed to "properly" recall extinction and failed to renew conditioned fear, and they also displayed reduced activation in the hippocampus and vmPFC (Garfinkel et al., 2014).

Subsequent studies from other laboratories have corroborated contextual processing deficits in PTSD. In a similar SCR fear conditioning paradigm, PTSD patients failed to "properly" renew conditioned fear when re-exposed to the conditioning context following full extinction that occurred 24 hours after the conditioning phase (Shvil et al., 2014: Impaired contextual modulation in post-traumatic stress disorder; presented at the 34th annual meeting of the Anxiety & Depression Association of America, March 28th, 2014). Another laboratory further corroborated these results by showing that PTSD patients failed to utilize a contextual "warning" cue in a stop signal anticipation task, supporting the idea that the context processing deficit in PTSD is general and not isolated to fear-processing (van Rooij et al., 2015).

In addition to modulating fear associated learning, contextual processing plays a key role in shaping memory processes, emotional responses and regulation, and in shaping flexible behavioral choices. As such, a context processing deficit based in dysfunction of a *hippocampal-prefrontal-thalamic* network could contribute to multiple aspect of post-traumatic psychopathology, beyond the documented specific deficits in extinction retention and fear renewal, and their associated symptomatology. For example, mPFC-Hpc circuitry creates associations between contexts, events, and corresponding emotional responses (Euston et al., 2012; Preston and Eichenbaum, 2013), so dysfunction in this system could link erroneous emotional contexts to a given situation, triggering emotional responses that are "inappropriate". For example erroneous retrieval of an intensely negative emotional context of loss and pain during normally joyful/happy events will prevent experiencing the joyful event as happy, which can be experienced as "emotional numbing". Similarly, excessive anger can emerge, following relatively innocuous triggers, if the context is perceived as dangerous or threatening. If context is identified as "unsafe", attention is focused on potential threat cues, leading to hypervigilance; but if contextual information that **should** alert one to danger is missed, this might lead to recklessness and retraumatization. Being "unmoored" from current contexts that keeps trauma memories from emerging in response to partial cues can lead to the emergence of intrusive memories. These hypothesized links between CP and a broad range of PTSD symptomology are speculative,

and extensive work is needed to test these ideas, but initial support linking connectivity within the CP circuit to specific PTSD symptoms has been emerging. For example, we have shown that diminished vmPFC/hippocampus connectivity at rest was associated with the severity of each of the three PTSD symptom clusters (i.e. intrusive, avoidant and hyperarousal), and that enhanced connectivity of these regions with SN regions was associated specifically with enhanced hyperarousal symptoms (Sripada et al., 2012). A more recent resting state connectivity study replicated these findings, reporting that re-experiencing symptoms in PTSD are linked to "disconnection" of hippocampus from right PFC, interpreted by the authors as a failure of contextualization and associated overgeneralization of trauma memories (Spielberg et al., 2015).

In addition to providing a broad and parsimonious explanation of PTSD symptoms, the CP model also provides a robust framework for integrating much of what is known, neurobiologically, about this disorder. The cellular and molecular processes that underlie context-processing have been revealed in animal studies (Maren et al., 2013). These data, coupled with data from animal models of PTSD (Knox et al., 2012) and human genetic and genomic studies support the relevance of context processing and its neurobiology to PTSD pathophysiology. For example, mediation of contextual fear depends upon activation of glucocorticoid receptors in prefrontal cortex (Reis et al., 2015). Glucocorticoid receptor (GR) hypersensitivity (with enhanced HPA negative feedback) has been repeatedly demonstrated in PTSD. Diminished mPFC function has also been consistently reported in PTSD (Shin and Liberzon, 2010) and confirmed by meta-analyses (Etkin and Wager, 2007). In our PTSD animal model (SPS), which successfully replicates the enhanced HPA negative feedback seen in patients (Yamamoto et al., 2009), abnormalities in fear renewal are also seen (Figure 5, top panel), and upregulation of glucocorticoid receptors in mPFC has been shown to be critical for expression of the PTSD-like phenotype (George et al., 2015). Similarly, glucocorticoid signaling in Hpc plays a critical role in pattern separation and can induce PTSD-like memory abnormalities in a mouse model (Kaouane et al., 2012); and in our SPS rat model, upregulation of GR in Hpc also appears critical to emergence of the PTSD-like phenotype (Knox et al., 2012). In concert, the emerging genetic and genomic findings in PTSD implicate molecular pathways that might alter hippocampal-prefrontal-thalamic circuitry – perhaps impacting hippocampal volume or context-relevant hippocampal function like neurogenesis and LTP. For example, polymorphisms in BDNF (Gatt et al., 2009; Aas et al., 2014), ADBR2 and FKBP5 (Fani et al., 2013), or methylation of *SLC6A4* (Dannlowski et al., 2014) or *FKBP5* (Fani et al., 2013), all have hippocampal effects, and each has evidence for association with PTSD. These findings resonate with reports of hippocampal size differences seen in PTSD, which may constitute a risk factor for PTSD development (Gilbertson et al., 2002; Bremner et al., 2003; Kitayama et al., 2005). Indeed, PTSD patients exhibit impaired performance on hippocampal-dependent tasks including visual memory recall tests and verbal memory tasks (R. J. Lindauer et al., 2006; Hayes et al., 2011), and these also may predate PTSD onset. Together these converging findings suggest a potential causative link between genetic and developmental factors that shape hippocampal-mPFC circuitry and the development of "signature" HPA abnormalities, and lead to contextual processing deficits that can create much of PTSD's phenomenology.

The CP model also nicely resonates with recent electrophysiologic and sleep findings. Hippocampal-prefrontal communication involves additional nodes in the midline thalamus, such as the reuniens and rhomboid nuclei, which participate in consolidation of enduring memories at a systems level (Pereira de Vasconcelos and Cassel, 2015). This process requires sleep-specific field-potential oscillations occurring during slow-wave rapid eye movement sleep (REM), which, in turn, rely upon specific function of locus coeruleus (LC) neurons (Vanderheyden et al., 2014). Thus effective encoding, consolidation, updating, and retrieval of contextual memory within hippocampal-prefrontal-thalamic circuitry likely require appropriate modulation by LC firing. This raises the possibility that adrenergic dysregulation, LC firing, and sleep problems might be contributing to disruption of the appropriate encoding and retrieval of contextual information, by affecting hippocampal-prefrontal communication. This is obviously only one potential etiologic pathway to mPFC-Hpc dysfunction (see below) and associated CP abnormalities, but these linkages pull adrenergic/autonomic function and sleep disruption into our context processing model, suggesting how sleep problems can play a key role in the emergence or perpetuation of CP deficits in a way that is consistent with sleep neurobiology in PTSD. Normal rewiring of memory networks in the hippocampus (including contextual memories) during sleep requires bidirectional plasticity (both synaptic strengthening (LTP) and weakening (DP) (Kemp and Manahan-Vaughan, 2004)) specifically during REM and transition to REM (TR). During REM and TR, to allow bi-directional plasticity (Poe et al., 2010), the noradrenergic (NE) neurons in the LC must turn off, which is essential for synaptic depotentiation (Thomas et al., 1996; Booth and Poe, 2006). If a hyperadrenergic state is present during REM and TR, the necessary synaptic depotentiation would be impaired, disrupting the rewiring of memory networks in the hippocampus (Vanderheyden et al., 2014), and potentially contributing to emergence of contextual processing abnormalities. The origins of the “hyperadrenergic state” could be partly genetic, given the ADRB2 findings in PTSD (Liberzon et al., 2014), which may thus contribute to development of deficits in hippocampal-prefrontal-thalamic circuit function. Indeed, there is evidence of linkage between disrupted REM and memory in PTSD (Lipinska et al., 2014) and evidence that REM abnormalities may play a mechanistic role in PTSD development (Marshall et al., 2014). It is also possible that pre-existing CP deficits, rooted in Hpc-mPFC circuit disruption after trauma exposure (recent or past), undermine adaptive, post-traumatic processing and contribute to the nocturnal hyperadrenergic state, disrupting sleep-dependent synaptic remodeling, and perpetuating and exacerbating the CP deficits. There are thus multiple potential etiologic pathways to Hpc-mPFC dysfunction and CP deficits, but the CP model does offer a parsimonious way to integrate longstanding evidence that PTSD involves sleep, ANS and HPA axis abnormalities, noradrenergic/HPA axis interaction effects on memory processes (Kukolja et al., 2011), and understanding of specific roles played by hippocampal-prefrontal-thalamic circuits in shaping episodic and contextual memory.

So what are the immediate implications and the next steps for development of the CP model, beyond improved conceptual coherence and explanatory power? A set of refutable hypothesis will need to be tested to enhance confidence in the model and demonstrate its utility in shaping future studies. First step will be to further document that the PTSD deficits seen in fear associated learning paradigms are also present in a broader range of tasks that

involve contextual processing and modulation. These include replication of fear renewal findings, and examination of fear reinstatement, contextual conditioning, and contextual modulation of responses to reward cues. Second, the hypothesized key role of Hpc-mPFC dysfunction should be examined by testing other Hpc-mPFC dependent functions in PTSD. These should include tasks that probe pattern separation and pattern completion capacities, visual-spatial navigation tasks, and tasks that require utilization of internal context (e.g., hunger, arousal). Finally the integrative, organizing concept of the CP deficit role predicts that other aspects of PTSD symptomatology, like emotional numbing, anger outbursts hypervigilance, etc. should be associated with CP deficits in both human studies and animal models.

Animal work will also be critical in determining the implications and value of this model, and it will require studies that directly examine contextual processing and Hpc-mPFC circuits. To date, animal studies have largely utilized paradigms rooted in fear conditioning/extinction with a focus on amygdala function. These paradigms have face-validity and have contributed a great deal, but it may be time to develop models rooted in other theory-based constructs like CP. These models may offer great value in translational and back-translational efforts. Indeed some steps in this direction have already been taken by various groups studying contextual processing (Jin and Maren, 2015), PTSD models (Knox et al., 2012) and glucocorticoid modulation of memory processes (Kaouane et al., 2012).

Conclusions and Implications

The identification of neural circuits involved in PTSD pathophysiology and the development of comprehensive models -- to link dysfunction in these circuits to existing established findings (genetic, neuroendocrine, immunolological, psychophysiologic) and to mechanisms of symptom development and disease maintenance -- is an ongoing effort that has gathered substantial momentum in the past decade. This signifies both a paradigm shift and remarkable progress in the trauma field, and clinical neuroscience in general, as similar brain-based comprehensive models of psychopathology have yet to be developed in the fields of schizophrenia, depression or bipolar disorder research, despite longer and better funded efforts. Our progress promises both early translational and longer-term conceptual and more fundamental scientific benefits.

Among the early translational/clinical benefits are potential advancements in development of more specific, mechanism-based treatments. If, as we suggest, PTSD is actually a collection of somewhat distinct neurobiological entities, with the FL, TD and EF models perhaps representing somewhat different endophenotypes, then identification of the dominant phenotype in a given patient might lead to a specific type of treatment, moving us towards a personalized medicine approach. For a patient with an “Altered FL” phenotype, enhancing extinction training by using a pharmacological enhancer (e.g., D-cycloserine) in conjunction with prolong exposure might be the most promising avenue. For an individual with a CP phenotype, use of glucocorticoid/adrenergic agents in combination with contextual processing “retraining” might be more promising. Individually tailored treatment packages could be further augmented by development of behavioral treatments specifically designed to strengthen contextualizing skills via enhanced function in Hpc-mPFC circuitry.

Improved pathophysiological models can also perhaps lead to better use of existing treatment strategies. For example, evidence for noradrenergic abnormalities in PTSD, along with evidence for their effects on memory, has led to efforts to treat or prevent PTSD using the beta receptor antagonist propranolol. Propranolol was administered immediately or soon after trauma exposure, to try to prevent consolidation of traumatic memories. While initial studies appeared promising (Pitman et al., 2002), subsequent reports did not support value of this approach (Sijbrandij et al., 2015). If, as the CP deficit model suggests, hyperadrenergic activity is most relevant to PTSD development during sleep, and REM in particular, the failure of some propranolol trials could be due to the wrong timing of propranolol administration. Adrenergic interventions might have to be directed toward nocturnal hyperadrenergic states. Similar logic might apply to attempts to treat/prevent PTSD using glucocorticoid administration. Glucocorticoids dose-dependently impacts learning processes with an inverted U-shaped dose-response curve (Salehi et al., 2010). Knowledge of a trauma exposed individual's glucocorticoid "status" could be essential to insuring beneficial effects, since "over-treatment" in some cases could enhance trauma memory consolidation or contribute to fear learning generalization. On the other hand, with appropriate understanding of the brain mechanisms involved, glucocorticoid administration could perhaps be used to enhance context processing capacities, allowing traumatic memory to be better contextualized, in a flexible way, facilitating an appropriate balance between mechanisms of pattern separation and pattern completion in the hippocampus. Indeed evidence that glucocorticoid administration may enhance efficacy of prolonged exposure therapy for PTSD has been recently reported, but efficacy depends on the individual's GC receptor sensitivity (Yehuda et al., 2015).

The long-term implications of this progress are more fundamental and more extensive. Developing comprehensive brain based models that describe abnormalities in memory deposition and retrieval as the result of specific neurobiological processes and molecular risk factors significantly advances our understanding of basic "cold" and "hot" memory mechanisms. It also deepens understanding of stress response systems and brain mechanisms underlying generation and modulation of emotions. This work has implications beyond PTSD translationally as well. The key brain pathways and physiological processes involved in PTSD pathophysiology likely have relevance to our understanding of other disorders, as well as stress sensitivity and resilience more generally. It is very unlikely that any psychiatric disorder can be fully explained by dysfunction of a single neurobiological circuit; and given the interconnected nature of these circuits, the disruption in functions of any particular circuit is likely to be seen in disorders, whose pathophysiology intersects with Hpc-mPFC circuits. Substance Dependence is one example, where contextual factors have already been invoked to explain relapse vulnerability (Crombag and Shaham, 2002). Exaggerated reactivity to drug cues, rather than trauma cues, may stem from CP deficits, in this case leading to abnormal approach behavior rather than the avoidance seen in PTSD. Determining the origins and roles of a particular Hpc-mPFC dysfunction in the etiological pathway of a specific disorder will require additional research, but examining CP broadly as a key brain function of relevance to a broad range of psychopathologies may facilitate progress.

As this work moves forward, we will be better able to define our disorders based on specific disruptions within particular brain circuits leading to impaired function, and this more precise, neurobiologically based understanding, will allow increasingly efficient, impactful, and individually tailored treatments. This progress will also slowly put to rest age-old debates about “nature vs. nurture” and “psychological vs. biological” in our study and understanding of psychiatric disorders, and thereby help to combat stigmatization and further open the door to better treatments for all who need them.

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Existing models of PTSD pathophysiology implicate neurocircuits subserving fear learning, salience detection, and emotion regulation. However, much remains unexplained. Liberzon and Abelson offer a novel, parsimonious model of hippocampal-prefrontal-thalamic dysregulation creating context processing deficits that contribute to PTSD symptom development.

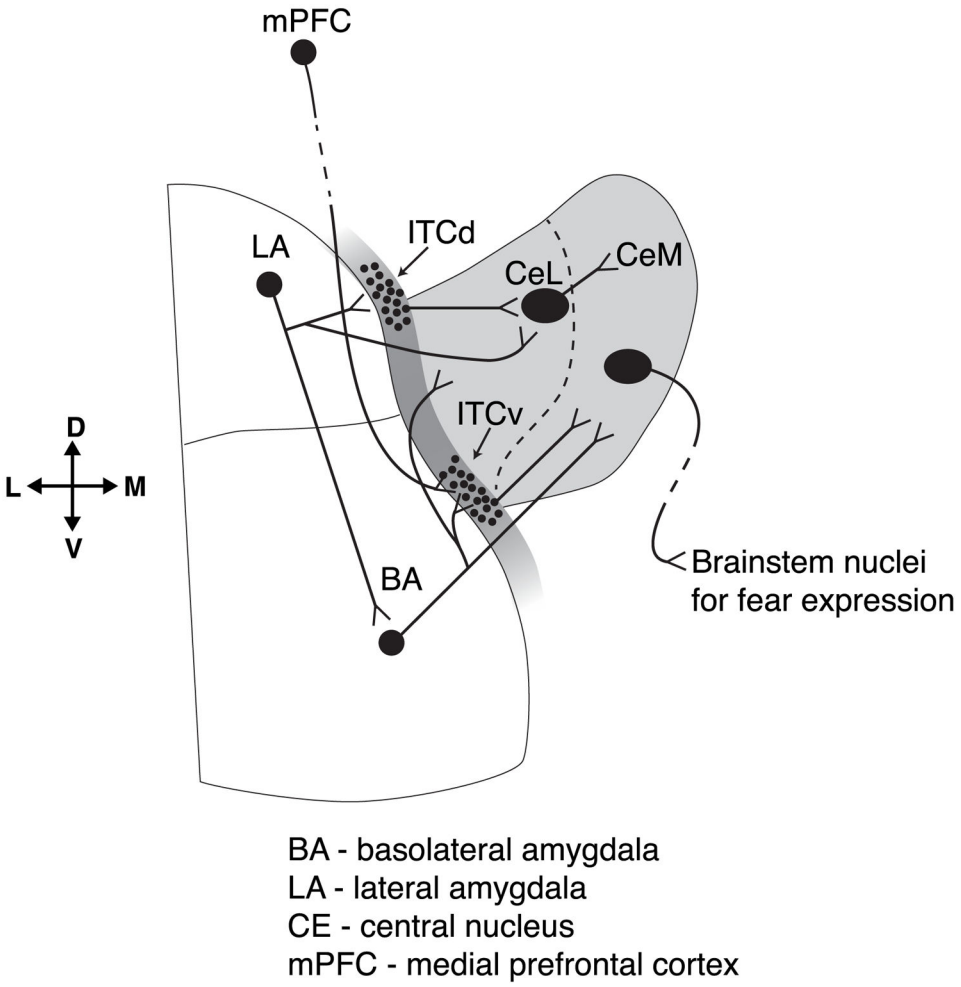

Figure 1.

Neural circuits within the Basolateral Complex (BLC) of the Amygdala. Altered functioning within BLC circuits has been implicated in the Abnormal Fear Learning model of PTSD (see text). Interrupted lines represent distal inputs to and outputs from BLC.

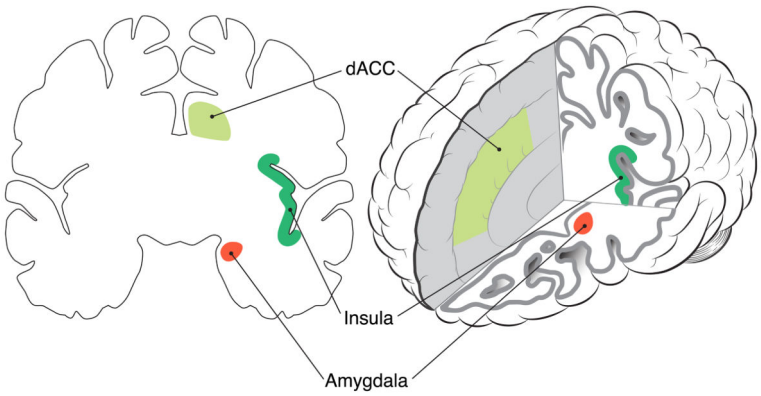

Figure 2.

Brain regions of the Salience Network. Abnormal function within Salience Network regions is implicated in the Exaggerated Threat Detection model of PTSD (see text).

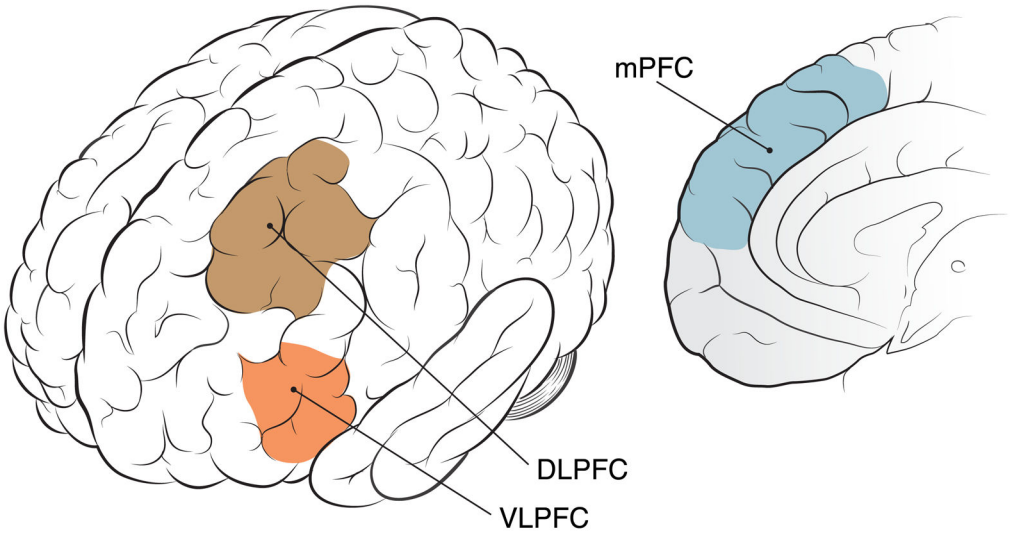

Figure 3.

Brain regions involved in executive function and emotional regulation. Abnormal function in these regions has been implicated in the Diminished Executive Function and Emotional Regulation model of PTSD (see text).

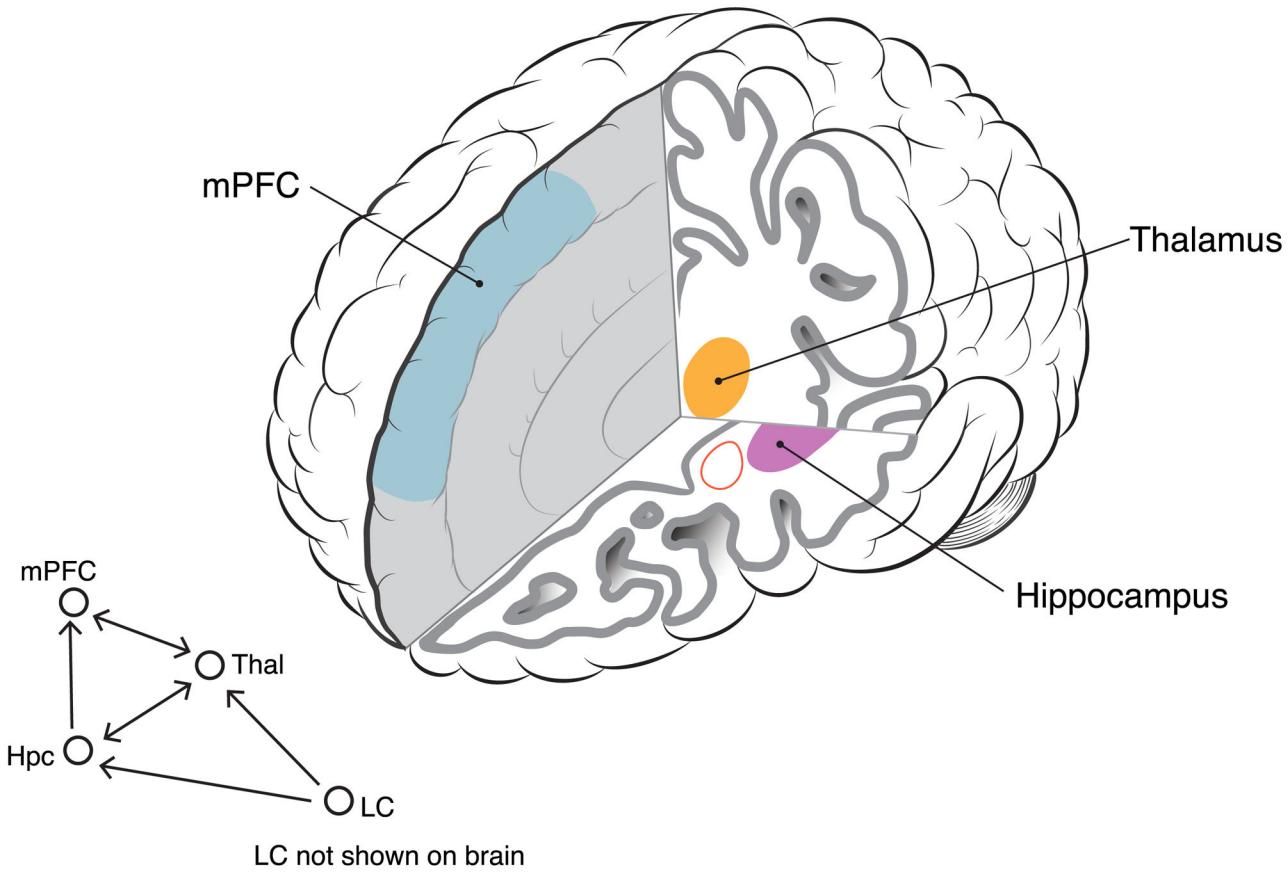

Figure 4.

Brain circuits involved in contextual processing functions. Abnormal function within these circuits is implicated in the Deficient Contextual Processing model of PTSD (see text). Information flow in this circuit includes Locus Coeruleus (LC) adrenergic neurons (shown in schematic but not visible in depicted brain slices).

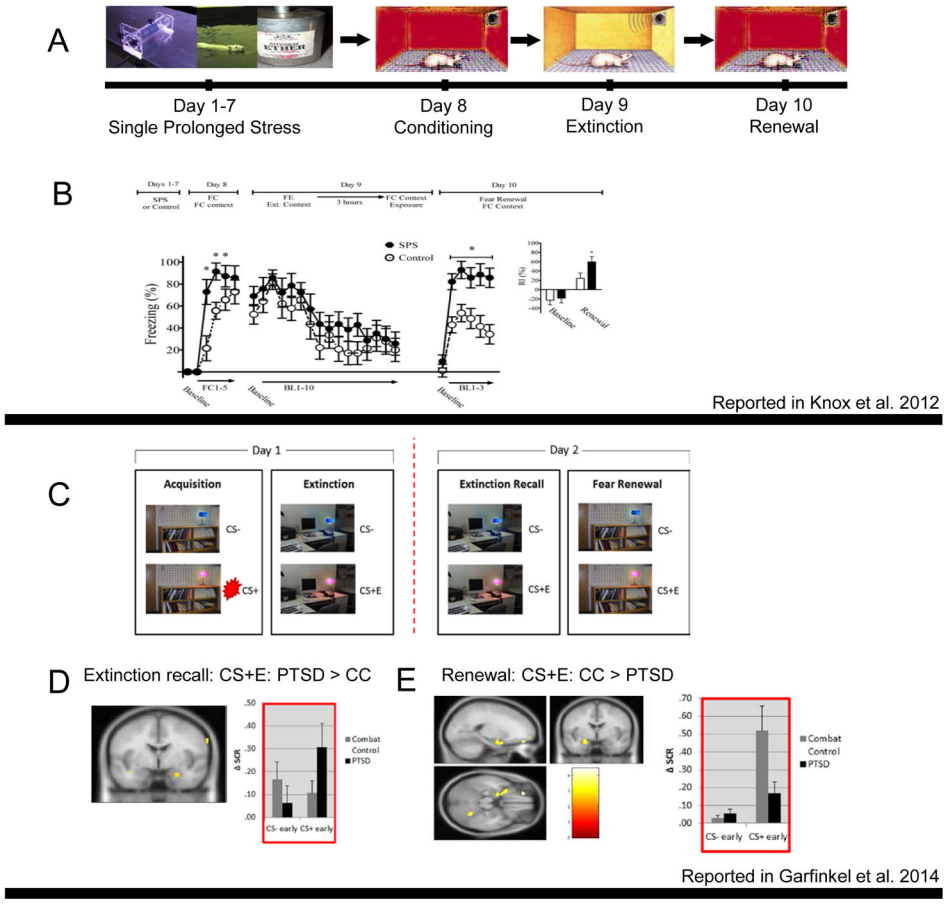

Figure 5.

Contextual processing abnormalities in the Single Prolonged Stress animal model of PTSD (Panels A and B) and in PTSD patients (Panels C, D and E). Panel A – Schematic depiction of the SPS paradigm, which involves multiple stressors delivered sequentially in one day and then a 7 day “rest” period, followed by fear conditioning, extinction and renewal testing. Panel B – data using this paradigm show abnormal fear renewal in SPS animals (seen on the right, in line graph and summary bar graph). Panel C – Schematic depiction (including screen shots) of the paradigm used to examine fear conditioning, extinction, extinction recall and fear renewal in fMRI experiments with humans. Panels D and E – data using this paradigm with PTSD patients and combat control (CC) subjects show abnormal extinction recall (D) and abnormal fear renewal (E) in PTSD (skin conductance data shown on right in both panels). Differences in fMRI activations in PTSD compared to controls, in response to previously conditioned and then extinguished stimuli (CS+E), are shown on the left in both panels.