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**A Unifying Translational Framework to Advance Treatment Research for Comorbid
PTSD and Substance Use Disorders**

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Abstract: We provide a translational unifying framework that can be used to synthesize extant lines of human laboratory research in four neurofunctional domains that underlie the co-occurrence of Posttraumatic Stress and Substance Use Disorders (PTSD+SUD). We draw upon the Alcohol and Addiction Research Domain Criteria (AARDOC) to include executive functioning, negative emotionality, reward, and added social cognition from the National Institute of Mental Health (NIMH) Research Domain Criteria into our framework. We review research findings across each of the four domains, emphasizing human experimental studies in PTSD, SUD, and PTSD+SUD for each domain. We also discuss the implications of research findings for treatment development by considering new ways of conceptualizing risk factors and outcomes at the level of the *individual patient*, which will enhance treatment matching and advance innovations in intervention.

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PTSD+SUD: Scope of Problem and Need for a Unifying Translational Framework

Posttraumatic stress disorder (PTSD) and substance use disorders (SUDs) are highly prevalent and debilitating disorders. Lifetime PTSD affects 7.7 million people, or 3.5% of Americans age 18 years and older (ADAA, 2018; NIMH, 2017). Further, in 2018, 20.3 million people, age 12 years and older, had an SUD (SAMSHA, 2019). The public health significance of each disorder on its own is undeniable due to their negative correlates and sequelae, including high levels of comorbid psychiatric disorders (Shen et al., 2020), high rates of attempted suicide, (Schneider, 2009), work impairment, (el-Guebaly et al., 2007), educational failure, and other adverse consequences. These findings are reflected in the escalating costs of PTSD and SUDs (Barkin et al., 2002), including annual productivity loss in excess of \$3 billion in the US due to work absences associated with PTSD (Greenberg et al., 1999), and annual costs of SUDs in the US exceeding \$740 billion in crime, productivity, and health care-related costs (National Institute on Drug Abuse, 2020). Although empirically-supported treatments (ESTs) exist for PTSD and SUDs alone, each is associated with significant unmet therapeutic needs: for example, nearly half of patients continue to meet criteria for PTSD following cognitive behavior therapy (CBT) (Bradley et al., 2005), and two thirds of adults with SUDs relapse within six months of treatment (e.g. McLellan, 2002).

The persistent co-occurrence of PTSD and SUD (PTSD+SUD) only compounds the significant public health problems these disorders pose. In individuals receiving treatment for a SUD, for example, the prevalence of co-occurring PTSD ranges from 26-43% (McCauley et al., 2012; Mills et al., 2006; Reynolds et al., 2011). Among those with PTSD, 40% have at least one SUD (e.g., Pietrzak et al., 2011). Those with comorbid PTSD and SUD (PTSD+SUD) typically are less responsive to treatment, as indicated by: higher rates of treatment non-completion, more

high risk behaviors like suicidal ideation and suicide attempts, higher rates of other comorbidities (e.g., depression, anxiety, or psychotic symptoms), increased polypharmacy, more frequent co-occurring medical problems, and more liable to suffer from symptom relapses compared to individuals with either disorder alone (Debell et al., 2014; Ouimette et al., 1997; Smith and Randall, 2012) . Those with PTSD+SUD may also suffer an increase in symptomatology when abstinent from substances, which can complicate the recovery process. In a maladaptive, reciprocally reinforcing process, PTSD symptoms can trigger increased substance use or misuse, which leads in turn to cyclical increases in PTSD symptoms (Back et al., 2006; Hien et al., 2010; Ralevski et al., 2014; Waldrop et al., 2007).

Recently, the advent of cross-diagnostic frameworks—most notably the Research Domain Operating Criteria (RDoC; Insel et al., 2010), and its counterpart, Alcohol and Addiction Research Domain Criteria (AARDoC; Litten et al., 2015) has prompted a search for unifying neurobehavioral understandings of psychiatric disorders and the variation inherent within diagnostic groups. Disturbances in executive functioning, awareness and regulation of emotions, reward and social cognition have all been consistently documented in chronic PTSD and implicated in comorbidities such as SUD that typically accompany and complicate PTSD prognoses (e.g., Aupperle et al., 2012; Koob & Volkow, 2016; Lanius et al., 2011; Le Berre, 2019; Ramey & Regier, 2019; Sharp et al., 2012; Stevens & Jovanovic, 2019). The convergence of these lines of research necessitate an integrated framework for studying the multiple domains affected by PTSD+SUD that can illuminate shared and overlapping mechanisms and advance personalized treatments (e.g., Cloitre et al., 2010).

The overall aim of this paper is therefore to review and synthesize recent advances in the conceptualization and experimental study of PTSD, SUD, and PTSD+SUD to support the development of a unifying translational framework. In the following review, we will:

- **Present** a set of four key PTSD, SUD, and PTSD+SUD neurofunctional domains and related constructs that can be used to facilitate translational research to identify mechanisms and heterogeneity in patients with PTSD+SUD.
- **Synthesize** experimental research across the four key neurofunctional domains with direct relevance to behavioral intervention research, highlighting innovations and emergent advances;
- **Demonstrate** how this unifying framework can be leveraged to optimize or facilitate neurobehavioral research with direct impacts on intervention development.

Unifying Conceptual Framework

Core Neurofunctional Domains in PTSD+SUD

As a unifying framework for translational studies of PTSD+SUD, we have identified *executive function*, *negative emotionality*, *reward*, and *social cognition* as key, neurofunctional domains and propose that these four domains be examined for their contributions to the emergence, maintenance, and functional outcomes of PTSD+SUD. See Figure 1. In the following sections, we review and synthesize for each domain relevant constructs, prevailing theory, and research from multiple units of analysis (behavioral, neural, genetic, etc.) that support its significance for PTSD+SUD.

Domain 1: Executive Function

Overview

Executive function (EF) refers to a set of higher-level cognitive processes responsible for the self-regulation of behavioral goals. EFs include processes related to sustained attention, working memory, decision making, inhibitory control, and cognitive flexibility (Diamond, 2013). Of these, inhibitory control – that is, the ability to inhibit (withhold) automatic responses (i.e., responses that are ready to be emitted or environmentally triggered) – is further divided into behavioral inhibition (i.e., self-control) and interference control (i.e., selective attention control or distractor suppression; (Aupperle et al., 2012; Diamond, 2013). EFs have received extensive examination in those with PTSD (Aupperle et al., 2012; Catarino et al., 2015) and SUD (Bernardin et al., 2014; Khemiri et al., 2019; Stavro et al., 2013). Individual differences in EF have been identified that either enhance or reduce risk for developing PTSD or SUD, as well as moderators of EF deficits in PTSD and SUD. These variables have demonstrable implications for engagement in and completion of psychosocial and pharmacological treatments (Bernardin et al., 2014; Broyd et al., 2016; Catarino et al., 2015).

Executive Functioning in PTSD

Numerous recent studies reveal that individuals with PTSD have significant EF deficits in attention, working memory, inhibitory control, and flexibility and planning (Aupperle et al., 2012; Polak et al., 2012; Scott et al., 2015; Woon et al., 2017). These cognitive deficits may index pre-trauma vulnerabilities that contribute to the development of PTSD or may be consequences or correlates of PTSD (Aupperle et al., 2012). Researchers theorize that pre-existing EF deficits may contribute to difficulty inhibiting attention to, or disengaging from, trauma-related memories and thoughts, enhancing the likelihood of developing or maintaining PTSD symptoms (Aupperle et al., 2012; Catarino et al., 2015). Conversely, the PTSD symptoms themselves, such as intrusion (e.g., intrusive thoughts and memories) and hyperarousal (e.g.,

sleep problems, concentration difficulties, etc.), may disrupt inhibitory and working memory functions contributing to EF deficits (Olf et al., 2014; Vasterling et al., 1998). Systematic reviews (Polak et al., 2012; 18 studies of 1,080 individuals) and meta-analyses (Scott et al., 2015 [60 studies of 4,108 participants]; Woon et al., 2017 [14 studies of 848 individuals]) of empirical studies of the link between PTSD and executive dysfunction, across multiple neurocognitive domains, revealed those with PTSD have poorer EF than either trauma-exposed individuals without PTSD or healthy controls. Polak and colleagues (2012) further showed that the link was amplified by type of trauma (combat), male sex, increased age, and greater depression severity. Nevertheless, due to the cross-sectional nature of most of the studies reviewed, it remains unclear whether EF deficits are pre-trauma vulnerabilities or consequences of PTSD (Olf et al., 2014; Polak et al., 2012).

Attentional Processing. While the EFs described earlier often require more effortful control, there are also implicit attentional processes (e.g., attentional bias), that often occur automatically, without conscious awareness, and are influenced by the emotional salience of the target of attention. For example, trauma-exposed individuals frequently exhibit a strong attentional bias toward the threatening stimuli in emotional Stroop tasks (e.g., Cisler & Koster 2010; Mueller et al., 2009; see Bar-Haim et al., 2007, for a review, but see Bremner et al. 2003; Shin et al., 2004), a tendency mollified after therapeutic intervention (El Khoury-Malhame et al., 2011) or in anticipation of fearful activities (Constans et al., 2004). However, attentional avoidance to threat-related stimuli in PTSD has also been consistently observed. In particular, individuals undergoing periods of severe stress, such as soldiers in simulated battle (Wald et al., 2011a), combat veterans with PTSD (Constans et al., 2004), or civilians under rocket fire (Bar-Haim et al., 2010), exhibit an attentional bias away from threat.

On the basis of these differences in performance, three different forms of attentional bias are potentially at play in PTSD: (1) *attentional facilitation* or increased sensitivity to trauma-related threatening stimuli; (2) *attentional interference* or difficulty disengaging from threatening material (Pineles et al., 2009; Weber, 2008); and (3) *attentional avoidance* or the tendency to move attention away from threat (Cisler and Koster, 2010). Attentional facilitation is seen in the enhanced speed and accuracy of PTSD participants in detecting threatening over non-threatening stimuli (e.g., during dot-probe performance, where participants are faster and more accurate to locate a dot that follows threatening vs. non-threatening stimuli appearing side-by-side; Cisler & Koster, 2010; Mueller et al., 2009; Shin et al., 2004; but see Bremner et al., 2003) Attentional interference is observed on tasks of sustained auditory or visual attention, including the continuous performance task (Shucard et al., 2008; Vasterling et al., 1998; Wu et al., 2010; see Aupperle et al., 2012 for a review). Increased attentional interference in PTSD has been observed equally in tasks employing threat-related stimuli, such as the emotional Stroop paradigm (Shin et al., 2001), or neutral stimuli, such as the Go/NoGo paradigm (Shucard et al., 2008). Attentional avoidance of threat on bias tasks is associated with a worsening of PTSD symptoms (e.g., Bar-Haim et al., 2010; Wald, Shechner, et al., 2011). These studies collectively suggest that attention processes in PTSD are nuanced and granular, with potential attentional biases towards, and difficulty disengaging from, threat in some contexts, and avoidance of threat in others.

Functional neuroimaging of PTSD participants during attention performance reveals abnormal activity, either hypo- and hyper-activity, in the ventromedial prefrontal cortex (vmPFC), anterior cingulate cortex (ACC), amygdala, and insula (Dickie et al., 2008; Fani et al., 2012;; Koenigs et al., 2008; Mazza et al., 2013; see Garfinkel & Liberzon, 2009, for review). Inefficient prefrontal control mechanisms in PTSD, combined with hyperactive amygdala

sensitivity, may instigate attentional biases to threat (Dickie et al., 2011; Mazza et al., 2013; Robinson et al., 2012). Analysis of event-related potentials (ERPs) reveals differences between PTSD and trauma-exposed participants in early gating of sensory information; as soon as 50 ms after stimulus onset; PTSD participants are deficient in suppressing repeated auditory stimulation (P50 suppression; Ghisolfi et al., 2004; Skinner et al., 1999; see Karl et al., 2006, for review). Electrophysiological indices (e.g., P300) also suggest that PTSD participants are poor in updating working memory of task-relevant information (Felmingham et al., 2002; Galleuy et al., 2001; see Tillman et al., 2013, for review).

The behavioral reports of attentional facilitation, attentional interference, or attentional avoidance in cognitive paradigms imply abnormal inhibitory control of task-irrelevant stimuli as a possible basis of bias effects (Cisler and Koster, 2010; Miyake et al., 2000). For example, dysregulated attentional control processes in PTSD may prevent attempts to disengage from threat (Cisler and Koster, 2010; Pineles et al., 2009, 2007), thereby harming efforts to focus exclusively on task-relevant stimuli. Alternatively, heightened inhibitory processes may yield hyper-regulation of efforts to ignore or avoid threat. Inhibitory dysregulation in threat avoidance may have its neural origin in hyperactivity within prefrontal or neighboring regions (Bryant et al., 2005; Fani et al., 2012; Lanius R et al., 2010). Taken together, literature points to a range of potential deficits to EF in PTSD, including explicit processes such as inhibitory control and implicit processes such as attentional facilitation, attentional interference, and attentional avoidance.

Executive Functioning in SUDs

As with PTSD, chronic, heavy substance use or SUDs have been associated with mild to large impairments in a range of executive functions including working memory, sustained

attention, learning, decision making, and inhibitory control across a variety of substances (e.g., alcohol, stimulants, cocaine, and cannabis) (Bernardin et al., 2014; Potvin et al., 2018, 2014; Stavro et al., 2013). The extent and severity of these deficits are often increased by earlier age of onset of use, increased frequency, quantity, and duration of use, and increased number of co-occurring psychiatric conditions (Nader and Sanchez, 2018; Volkow et al., 2016).

Stavro and colleagues (2013) conducted a meta-analysis of 62 studies of 5,302 individuals with alcohol use disorders and found evidence of widespread impairments across 11 of 12 cognitive domains (verbal fluency/language, speed of processing, working memory, attention, problem solving/executive functions, inhibition/impulsivity, verbal learning, verbal memory, visual learning, visual memory and visuospatial abilities). Potvin and colleagues (2018) conducted a meta-analysis of 44 studies of 1592 individuals with methamphetamine use disorder (MUD) and found that, compared with 1820 healthy controls, those with MUD had large and significant deficits in reward processing, impulsivity, and social cognition and moderate deficits in global cognition, attention, executive functions, language/verbal fluency, verbal learning and memory, visual memory, and working memory. Potvin, Stavro and colleagues (2014) used meta-analysis across 46 studies to assess cognitive dysfunction in individuals with cocaine use/dependence. The authors reported moderate impairment during abstinence in the domains of attention, impulsivity, and working memory. Acute and chronic cannabis use has been shown to be associated with deficits in attention, working memory, verbal learning, and inhibitory control (Crean et al., 2011; Solowij et al., 2002). A recent systematic review of 105 studies published from 2004-2015, found both acute and chronic effects of cannabis use on various measures of cognitive functioning; although the evidence was mixed for

cannabis' impact on executive functioning and decision making as well as whether recovery of cognitive functions is possible with abstinence (Broyd et al., 2016).

Attentional processing. As with PTSD, implicit attentional processes are also at play in SUD. Among substance users, regular cannabis users have demonstrated an attentional bias to and maintained their gaze longer on cannabis cues, evaluated cannabis cues as more pleasant, and displayed greater approach tendencies toward cannabis cues than neutral cues (Cousijn et al., 2013; Field et al., 2006; Gray et al., 2008). Moreover, attentional bias in cannabis users is positively associated with frequency of cannabis use (Field et al., 2004). Robust attentional biases to substance-related cues, compared to neutral cues, have also been found among those with alcohol use disorders (Sinclair et al., 2010), cocaine use disorder (Leeman et al., 2014), and opioid use disorders (Constantinou et al., 2010; Garland, 2013). Moreover, attentional bias has been found to be elevated before temptations to use in heroin and cocaine users (Waters et al., 2012) and individuals with high levels of subjective craving or who have SUDs are more likely to demonstrate attentional biases than their counterparts with lower levels of craving or no or less severe SUDs (Field et al., 2013, 2009, 2006, 2004; Leeman et al., 2014).

Overall, extant evidence indicates that SUDs are associated with significant impairments in cognitive functioning in general and EF (both explicit and implicit), in particular. Yet given the significant heterogeneity in type of participants with SUD, how frequency/quantity/duration of substance use was assessed, whether participants currently use substances or are in different phases of treatment, and whether co-occurring substance use was assessed and controlled, more research is needed to confirm and extend existing findings (Broyd et al., 2016).

Several hypotheses have been proposed to explain the cognitive deficits found among those with SUDs. The *high-risk hypothesis* claims that in the development of SUD, pre-existing

vulnerabilities toward cognitive deficits contribute to the transition from recreational substance use to misuse (Cadet and Bisagno, 2016). For example, poorer cognitive functions in areas such as impulsivity and decision-making may influence the degree to which an individual engages in substance use and other risky behaviors; pre-existing impairments in inhibitory control may also contribute to loss of control over behavioral impulses to use substances, which may contribute to excessive use and eventual development of use disorders (Potvin et al., 2018). Alternatively, EF deficits may be *consequences* of structural and functional changes in the brain secondary to chronic substance use (Baler and Volkow, 2006; Cadet and Bisagno, 2016). Most substances are known to have toxic effects on the brain causing structural and functional changes in neural functioning (e.g., altering dopamine, GABA, glutamate, cannabinoid, and opiate receptor functioning) (Baler and Volkow, 2006), which may lead to cognitive deficits. EF disruptions are most likely to be seen during the preoccupation/anticipation stage of addiction (Koob and Volkow, 2016, 2010), owing to compromised prefrontal activity, contributing to the impulsive and compulsive nature of substance seeking and using. Collectively, as with PTSD, extensive research implicates a range of EF deficits in SUD, including abnormalities in working memory, attention, learning, decision making, inhibitory control, reward processing, and impulse control. It is noteworthy that, unlike PTSD, recovery of cognitive function in SUD has frequently been reported, particularly during periods of extended abstinence (Hanson et al., 2011; Verdejo-Garcia et al., 2019). Whether lingering deficits increase proclivity to, or reflect consequences of, substance use, or both, remains unclear.

Executive Functioning in PTSD+SUD

Given the separate effects of PTSD and SUD on EF deficits, and the substantial number of individuals with PTSD who have comorbid SUD, one might expect PTSD+SUD to be

associated with greater levels of EF impairments. However, *no studies to date* have tested this hypothesis in a sample with co-occurring PTSD+SUD. More studies have focused on implicit attentional processes and their contribution to the PTSD+SUD comorbidity. For example, one study revealed that cocaine dependent individuals with PTSD displayed a greater attentional bias toward cocaine cues after exposure to a trauma-related script, highlighting the role of cognitive processes in the link between these two disorders (Tull et al., 2011). Another study found that, compared to individuals with cocaine dependence only and to healthy controls, individuals with co-occurring PTSD and cocaine dependence, were more reactive to both drug- and trauma-related visual cues (Sokhadze et al., 2008). The authors speculated that attentional bias and reactivity to both drug and trauma-related cues may contribute to an enhanced vulnerability to using drugs to cope, particularly in the context of executive function/ inhibitory control deficits (Sokhadze et al., 2008). Overall, studies highlight the importance of automatic/implicit processes in the onset and maintenance of both PTSD and SUD. More longitudinal studies are needed, however, in order to tease apart onset, course, causes, and consequences of the relationship between PTSD, SUD, and executive dysfunction.

Domain 2: Negative Emotionality

Overview

Negative emotionality refers to disruptions in the emotional reactions of fear, sadness, and other negative emotions. It includes responses to varying levels of stress: from acute threat (fear) and potential threat (anxiety) to sustained, chronic stress. Affective responses to stress may involve not only fear but a host of other negative emotions such as anger and sadness.

Additionally, negative emotionality extends to processes related to coping with the broad concept of loss, be it loss of a person, or internal state such as loss of a sense of control. Negative

emotionality is included in the RDOC domain of Negative Valence Systems, which pertains to the coordinated systems of emotion, behavior, motivation, and cognition activated in response to negative environments or stimuli, such as threat or loss (Insel et al., 2010).

As mediator of an individual's self-preserving response, the brain's stress system is a calibrated network of neurochemical processes reactive to acute and sustained stress. *Negative emotionality* is a component of the stress system. The neurotransmitter systems of glucocorticoids, corticotropin releasing factor (CRF), norepinephrine, and dynorphin are known to be critical in regulating stress responses (see Koob, 2008 for review). In situations of acute stress, activation of the HPA and the sympathetic-adrenal-medullary (SAM) occurs. In contexts of chronic and repeated stress where repetitive or sustained activation of the HPA system occurs, the stress system is known to adapt in a number of ways by either a blunted (disrupted HPA axis activation) response or a prolonged one (disrupted HPA axis inhibition) and failure to habituate to the stressor (McEwen, 2008). Several neurobiological pathways contribute to HPA axis activity. The HPA axis is inhibited by the prefrontal cortex and the hippocampus; CRF neurons are stimulated by the amygdala. In the extended amygdala, CRF and dynorphin trigger the brain stress response, producing the experience of anxiety-like and dysphoric states, and are strongly implicated in fear-conditioning and pain processing (see Koob, 2008).

Negative emotionality in PTSD

PTSD has been conceptualized as a “stress-induced fear circuitry disorder,” (Shin and Handwerker, 2009): a pathology rooted in a dysregulated fear response, specifically, the inability to inhibit fear (Jovanovic and Ressler, 2010). Closely related to fear— although considered to represent an alternative model of, and pathway, to PTSD— are dysregulations consistently found

in the processing and regulation of other negative emotions—such as anger, sadness, shame, and guilt (Lanius et al., 2010).

Drawing from Pavlovian conditioning paradigms, animal and human studies have reliably modeled PTSD as a disorder of fear inhibition (VanElzakker et al., 2014). During fear acquisition, a neutral stimulus is paired with an aversive unconditioned stimulus and, through repeated paired exposures, triggers a similar response to the aversive stimulus. Then, either through extinction or conditioned inhibition, an individual learns that a stimulus once paired with an aversive stimulus is no longer dangerous. Importantly, the conditioned response is not forgotten, but rather is superseded by new learning. In human laboratory models, research has demonstrated that individuals with PTSD show marked deficits in the ability to inhibit conditioned fear responses, showing significantly weaker reductions in acoustic startle and galvanic skin responses than control groups (i.e. Grillon & Morgan, 1999; Peri et al., 2000). In a recent meta-analysis (Duits et al., 2015) of 44 fear extinction studies with predominantly PTSD samples, a small/medium effect size ($d = 0.35$) was found for delayed or reduced fear extinction (unlearning of a conditioned fear response) in PTSD patients versus controls. Specifically, individuals with PTSD may extinguish startle only under conditions of paired stimuli or never-paired stimuli, but *not* to the originally aversive stimulus (Jovanovic et al., 2010; Jovanović et al., 2007). In addition to disrupted extinction learning, studies have found alterations in other aspects of fear conditioning. PTSD has been associated with a heightened ability to discriminate between aversive and safe stimuli (Orr et al., 2000; Wessa and Flor, 2007) and rather than an altered extinction learning style, a shorter length of extinction retention (Milad et al., 2008). These studies collectively suggest that PTSD is characterized by diminished extinction learning, at least to original aversive cues.

On a fear conditioning account, PTSD can be conceptualized as the learned “hijacking” of the brain’s fear circuitry. Disruptions in amygdala activity have been consistently associated with the disorder, with evidence for both hyperactive and hypoactive amygdala responses. Amygdala hyperactivity in PTSD is driven by a complimentary hypoactivity in the vmPFC (Liberzon and Sripada, 2007; Shin et al., 2006); although see (Gilboa et al., 2004; St. Jacques et al., 2011) Demonstrative of this, in a series of studies, Milad et al. (2008, 2009) found greater activation in the amygdala in PTSD relative to controls during extinction learning and reduced activity in vmPFC and hippocampal regions during extinction learning recall.

The fear extinction learning model of PTSD considers disruptions in the neurocircuitry of fear to underlie the stress sensitization that accompanies PTSD. The hippocampus and vmPFC are prime modulators of the stress response through their inhibition of amygdala response. Evidence of reduced hippocampal and ACC volume have been found in PTSD samples (Bremner et al., 2007; Corbo et al., 2005; Woodward et al., 2006) as well as reduced activity in the mPFC in PTSD patients shown trauma-related and non-trauma related negative stimuli (Britton et al., 2005; Lanius et al., 2003). On a neurochemical level, Yehuda (1993) suggests that this sensitization sequence is observed in a disruption of the cortisol feedback loop—the reduction of cortisol posttrauma enhances the release of CRF and NE, prolonging and sensitizing the stress response. Indeed, various studies have documented low basal cortisol and exaggerated cortisol response to new stress, although inconsistencies in the literature point to differences in biological, social, and psychological factors amongst the studied groups (Gilpin and Weiner, 2017). This body of literature clearly implicates impaired extinction learning, and consequential sensitization of stress responses, as a core feature of PTSD that leads to its symptomatology.

Emotional dysregulation. Dysregulation of the fear circuitry may also trigger disruptions in the neural processing of other negative emotions, and suggests a route through which fear leads to alterations in more general regulation of emotions (Lanius et al., 2010). In addition to modulating fear responses, the hippocampus, vmPFC, ACC, and amygdala have all been linked to the regulation of anger, guilt, and shame as well as broad emotion regulation functions such as perception, suppression, and arousal. This has led some to propose that fear dysregulation may co-opt top-down emotion processing centers causing general emotion dysregulation issues (Lanius et al., 2010).

Support for this view is found in studies documenting significant emotion dysregulation in PTSD (Chang et al., 2018; Doolan et al., 2017; Weiss et al., 2018). For example, studies have examined whether these disorders are characterized by heightened emotional reactivity, that is, relatively greater change from baseline in emotional intensity following provocation (Linehan, 1993). PTSD research is mixed with respect to whether individuals with PTSD exhibit heightened emotional reactivity compared with control groups, with some self-report and physiological research supporting it (e.g., Butler et al., 2019), others indicating that PTSD is characterized by hypo-reactivity (e.g., Woodward et al., 2015), and some showing no differences at all (e.g., DiGangi et al., 2017), compared with control groups. However, neuroimaging meta-analyses and studies show that individuals with PTSD have some abnormalities in emotion systems relative to controls, including reduced amygdala volume and heightened amygdala and insula activation in response to emotion provocations, compared with controls (Driessen et al., 2004; Karl et al., 2006; Mazza et al., 2013; Patel et al., 2012; Ramage et al., 2015).

In addition to disrupted emotionality, recent research suggests broader deficits in emotion regulation (i.e., the intentional or automatic modulation of emotion; Gross & Thompson, 2007)

in PTSD. Self-report studies suggest that emotion regulation deficits are relatively higher in PTSD (e.g., Chang et al., 2018; Doolan et al., 2017; Weiss et al., 2018). Yet experimental studies examining emotion regulation in PTSD yield mixed findings relative to controls, with some indicating that individuals with PTSD have reduced ability to use strategies to decrease emotion (e.g., New et al., 2009; Xiong et al., 2013) and others indicating no difference (e.g., Fitzgerald et al., 2016; Rabinak et al., 2014; Woodward et al., 2015).

Nevertheless, neurobiological research reveals significantly reduced activation in emotion regulatory brain regions in PTSD relative to controls when participants attempt or prepare to regulate emotion (Butler et al., 2019; Mazza et al., 2013; New et al., 2009; Patel et al., 2012; Rabinak et al., 2014; Xiong et al., 2013). Structural reductions in brain volume (e.g., Karl et al., 2006), gray matter (e.g., Kühn & Gallinat, 2013), and white matter integrity (e.g., Olson et al., 2017) are shown in PTSD groups relative to controls. Finally, studies suggest reduced functional connectivity between frontal emotion regulatory and emotional neural brain regions in PTSD (Clancy et al., 2017; Shin and Handwerker, 2009). Taken together, literature suggests that there are several disrupted emotion systems in PTSD. Specifically, individuals with PTSD may exhibit impairments in extinction learning, which may have downstream effects on other emotion systems. Indeed, individuals with PTSD may exhibit heightened stress responses and emotional reactivity, and deficits in regulating those results. Such emotion regulatory deficits may have a neural signature as indicated by decreased functioning in neural emotion regulatory regions, although future research will be needed to explore this hypothesis.

Negative emotionality in SUD

The self-medication model of SUD posits that alleviation of negative affect is a driving force in the use of substances (Khantzian, 1997). Research indicates that individuals with SUDs

report higher rates of arousal to unpleasant images (Aguilar De Arcos et al., 2008) and greater difficulties regulating negative affective states such as sadness and anger (Fox et al., 2008) than controls. Indeed, across all drug types, an underlying characteristic of addiction is the presence of negative mood states in the wake of acute and prolonged abstinence (APA, 2013).

Furthermore, a broad base of animal and human research has shown that, across drug classes, stress promotes earlier and greater likelihood of initiation of use, higher risk of regular and then disordered use and, following the emergence of drug-related pathology, lower motivation to stop, and increased risk and frequency of relapse (see Lijffijt et al., 2014; Logrip et al., 2012; Mantsch et al., 2016 for comprehensive reviews).

From the perspective of the three-stage cycle of addiction (Koob and Le Moal, 1997) employed by the AARDOC framework, negative emotionality is central to one of two pathological reinforcement loops that over time leads to problematic and eventual disordered use. The first stage of the addiction cycle (*binge/intoxication*) reflects a positive reinforcement process, wherein the positive consequences of the drug use increases the likelihood of its use. During the second stage (*withdrawal/negative affect*), coined the “dark side of addiction” (Koob et al., 2014), craving and use occur in the service of a negative reinforcement process, recruited to mitigate the aversive states encountered by the user during substance withdrawal and concomitant negative mood states such as dysphoria, anhedonia, anxiety, and irritability. Important to our later discussion of PTSD+SUD and reward/incentive salience, the transition from the first to second stage of the addiction cycle—from impulsive to compulsive use—is hypothesized to proceed through the disruption of homeostasis between its reward and anti-reward systems (Koob and Le Moal, 2008) alongside a sensitization of the brain’s stress system.

Sensitization of the stress system is considered to be a fundamental, underlying mechanism in the relationship between negative emotionality and SUDs. In animal studies, the prolonged administration of all major drug types produces dysregulations in the HPA axes and the CRF-mediated extrahypothalamic stress systems; during acute withdrawal, elevations in adrenocorticotrophic hormone, corticosterone, and amygdala CRF have been consistently observed (see Koob et al., 2014 for review). Importantly, the stress sensitization associated with chronic substance use may originate with this HPA response, which in turn activates the extended amygdala where increases in CRF induce stress- and fear-like states. This hypothesis is supported by a wealth of animal research. For instance, CRF antagonists have been shown to remove distress produced by withdrawal or abstinence after prolonged administration of cocaine, opioids, and alcohol (see Koob et al., 2014). Ultimately, as drug use progresses from recreational to compulsive, a “cascade of changes” (p. 11, Koob et al., 2014) leads to a significant overactivation of the brain’s stress systems and the creation of a “feed-forward” loop wherein stress triggers further use, which further sensitizes the stress system.

Experimental behavioral research corroborates a heightened stress response and heightened emotional reactivity in response to emotional provocations in individuals with SUD relative to controls (Aguilar De Arcos et al., 2008; Moberg et al., 2017). Substance use also predicts heightened emotional reactivity in those at risk for developing SUDs (Tomko et al., 2017). However, neuroimaging research in SUD is more mixed, suggesting that individuals with SUD or problematic substance use exhibit heightened (e.g., Gilman & Hommer, 2008; Potenza et al., 2012) or reduced (e.g., Heitzeg et al., 2015; Salloum et al., 2007) activation in emotion regions such as the amygdala and insula in response to stressors or substance cues relative to controls.

Such mixed findings have led some theorists to suggest that potential alterations in these emotion regions are driven by abnormalities in the prefrontal regions that regulate them, rather than the limbic regions themselves (Wilcox et al., 2016). Indeed, several studies suggest that individuals with SUD or problematic substance use exhibit reduced activation of emotion regulatory regions (e.g., dorsolateral and dorsomedial prefrontal cortex) in response to emotion stimuli relative to controls (e.g., Asensio et al., 2010; Seo et al., 2016). Furthermore, as with PTSD, studies suggest that individuals with SUD, or who engage in greater substance use, exhibit reduced functional connectivity in frontal and emotion regions (e.g., amygdala) during emotion regulation and resting state paradigms (e.g., Crane et al., 2018; Seo et al., 2016; Zimmermann et al., 2017). In contrast, some studies display the opposite effect, revealing increased connectivity between frontal regions and the amygdala during resting state and emotion elicitation paradigms (e.g., Contreras-Rodríguez et al., 2016; Zimmermann et al., 2018). Research therefore implicates heightened emotional response processes in SUD, but is mixed with regards to whether and how emotion regulation is deficient in the disorder.

Negative emotionality in PTSD+SUD

There is considerable consensus that PTSD+SUD may be characterized by hyperarousal and hypersensitivity to stress (Gilpin and Weiner, 2017). However, to date, no profiling of the potential specific HPA-axis dysfunctions related to this comorbidity has been conducted. In terms of emotion regulation, few studies have examined emotion dysregulation processes in a PTSD+SUD group. In one such study, trauma-exposed SUD patients listened to personalized trauma scripts and provided reports of the emotion regulation strategies that they used during it, as well as self-reported and cortisol measures of negative affect. Higher levels of PTSD severity predicted greater use of both adaptive and maladaptive strategies. Higher PTSD severity also

predicted greater emotional reactivity to the trauma cues, but the direction of this relationship varied based on the specific emotion regulation strategies employed (Tull et al., 2018). These findings suggest that both PTSD and the specific forms of emotion regulation studied predict emotion and emotion regulation processes in SUD. It is possible that the research examining emotion regulation in SUD is mixed due to a failure to control for these findings. Taken together, studies suggest a need for further investigation into the impact of PTSD and specific emotion regulation strategies on emotion dysregulation processes in SUD. Although research converges in suggesting that these populations are characterized by emotion dysregulation, the exact nature of these problems remains unclear.

Domain 3: Reward Functioning

Overview

Reward functioning is a multidimensional psychological construct involving the ability to seek out and enjoy stimuli of positive motivational valence. The construct has well specified neural substrates and circuitry (Nawijn et al., 2015) that have been widely studied in both animal and human models (e.g., Hyman et al., 2006; Koob & Volkow, 2010). Drawn from RDoCs conceptualization of the Positive Valence Systems, reward is viewed as having three primary components: 1. Initial/Sustained Responsiveness to Reward (“liking”), 2. Approach Motivation (“wanting”) and 3. Reward Learning (“habit”) (Baskin-Sommers and Foti, 2015; Insel et al., 2010; Nawijn et al., 2015; Vujanovic et al., 2017). We note that incentive salience is a component of reward functioning that “transforms the perception of stimuli, imbuing them with salience, and making them attractive” (Kwako et al., 2016). Motivation, conditioned reinforcement, attentional biases and cue reactivity are all components of incentive salience that

are involved in approach/motivation and reward learning, as well as with circuitry shared with the prefrontal regions involved in reward processing.

The reward system is involved in the development and maintenance of PTSD as well as SUDs, and has been proposed as a core system characterizing transdiagnostic clinical problems (Baskin-Sommers and Foti, 2015). Emerging research in PTSD and SUD independently and together suggest that individual differences in reward processing, and a key related process, incentive salience, may help to account for heterogeneity in both diagnosis and treatment response, and provide new insights into understanding the course of PTSD+SUD and potential future treatment targets.

Anhedonia, or the lack of ability to experience pleasure accompanied by decreases in motivation, also involves the reward system; indeed, dysfunction in reward processing may be viewed through the lens of anhedonia (e.g., Der-Avakian & Markou, 2012; Garfield et al., 2014). This conceptualization of anhedonia has been applied to the study of PTSD using the fear extinction model, which posits that associative learning of fear-related cues and the failure of extinction learning lead to the maintenance of posttraumatic symptoms (Nawijn et al., 2015; Vujanovic et al., 2017). Anhedonia is also proposed as a central feature involved in the maintenance of SUDs, linked with dysfunction in the brains reward systems for those with addictions (e.g., Koob & Volkow, 2010, 2016).

Beyond anhedonia, however, there are a number of other ways to conceptualize reward. Deficits in the ability to anticipate or predict expected rewards, other values and costs associated with rewards have been used to study reward processing in both PTSD and SUD populations. Similarly, the amount of effort expended to obtain a reward, decision-making and other factors associated with expending effort, such as motivation, have also been used to conceptualize

reward. Motivation to obtain a reward has also been studied. (Der-Avakian & Marcku 2012). Since there appear to be distinct neural processes and substrates involved in each of the three domains of reward functioning (“liking”, “wanting” and “habit”), conceptualization and measurement of each of the domains will lead to more specificity in understanding reward functioning within particular individuals or diagnostic groupings, and is particularly critical for studying the overlap between these areas in comorbidity of PTSD+SUD.

Reward Functioning in PTSD

Models characterizing PTSD as disruptions in extinction learning after trauma exposure (e.g., Milad et al., 2009; Papini et al., 2015) suggest possible related deficits in reward learning: Stimuli that would typically be paired with hedonistic, positive valence are not. Here, deficits in reward learning sustain fear and threat responsiveness in PTSD. In fact, among those with PTSD, reward deficits have generally been observed in each of the two domains of “liking” and “wanting.” Nawijn et al. (2015), in a systematic review of 29 studies of reward processing in individuals with PTSD and anhedonia, identified that those with PTSD show decreased responsiveness to rewards compared to healthy controls, as well as decreased effortful approach towards rewards. These findings in reward functioning suggest deficits in experiences of “liking” are dampened in those with PTSD compared to controls (MacNamara et al., 2013; Steuwe et al., 2012) when comparing positive facial stimuli. The motivational “wanting” domain, assessed via behavioral tasks such as monetary rewards and facial stimuli ratings, (Casada and Roache, 2006; Elman et al., 2005; Hopper et al., 2008) has also been shown to be diminished in PTSD compared to controls. However, since symptoms of anhedonia were used in this systematic review as a proxy for reward processing deficits (i.e., a dimensional model for PTSD focusing on anhedonia as distinct from other PTSD symptoms such as externalizing, re-experiencing

symptoms, and hyperarousal) (Liu et al., 2011), broadening constructs of study to include constructs such as cue reactivity, incentive salience, and delay discounting will also help to illuminate a more complete picture of reward deficits found in PTSD.

In one neuroimaging study on motivation and decision-making tasks involving gains and losses (Sailer et al., 2008), those with PTSD showed lowered activation in two parts of the brain implicated in the reward system—the prefrontal cortex (a region involved in decision-making processes) and the nucleus accumbens, part of the mesolimbic dopaminergic pathway and a core area with circuits and projections to striatal-thalamic and cortical pathways involved in the regulation of motivation and affect. Further, those with PTSD showed lowered responsiveness to gains and equal responsiveness to losses compared with controls. This differential was suggested to be associated with motivational reward deficits seen in PTSD. The findings highlighted the importance of considering decision-making, gesturing to novel possibilities for studying behavioral economics and neuroeconomics in relation to PTSD.

On the other hand, another study (Myers et al., 2013), examining the degree to which rewards and punishments impacted learning in veterans with and without self-reported PTSD symptoms, found that those with high PTSD symptoms actually performed better than the control group on reward-based trials in a probabilistic categorization task (with rewards and punishment trials pre-set), and were equivalent to controls on punishment-based trials. In contrast, the controls demonstrated more responsivity than those with high PTSD symptoms on ambiguous trials, suggesting that the neutral trials were only reinforcing for the controls. Collectively, the findings points to decreased responsiveness to, and effortful approach of reward, and possibly implicates broader deficits in decision making and motivation in PTSD.

Reward Deficits in SUD

In contrast to the dampened responsiveness and approach motivation of anhedonia seen in PTSD, in the early addiction process, natural rewards are thought to be overtaken by alcohol and drug effects, leading to a hyperactive reward circuit (Baskin-Sommers and Foti, 2015; Blum et al., 1996; Stice et al., 2013; Stice and Yokum, 2014). Where positive rewards such as hedonia (pleasure) are thought to drive the development of addiction in the earlier stages (“liking”), later stages suggest that withdrawal symptoms, craving, and negative affect are implicated in the relapse process and maintenance of addictions (e.g., Koob & Volkow, 2010). Robinson and Berridge (1993, 2013) conceptualize the development of a SUD after multiple exposures to substances as involving a change from the state of “liking” to a state of “wanting.” The *incentive salience hypothesis* (Robinson & Berridge, 1993) posits that through associative learning, paired with dopaminergic sensitization of the neural structures in the mesolimbic-striatal reward system (nucleus accumbens, ventral tegmental area, striatum), drug-seeking behavior is shaped by motivation, conditioned reinforcers (cues), and craving. Through associative or reward learning (Morales et al., 2018), the consumption of substances leads to increased reward (i.e., feeling pleasure, reducing anhedonia), which is associated with interoceptive and external cues, and contexts, that later motivate the individual to seek the substance, increasing its incentive salience (Hyman et al., 2006; Koob and Volkow, 2016).

Reward processing dysfunction in SUDs is among the most widely and well-studied transdiagnostic, translational constructs with clear and well-developed models across animals and humans. These models encompass behavioral/experimental paradigms and apply techniques and methods that span assessment of behavior, task-based reward mechanisms of the three domains of reward (initial approach, motivation and learning), and neural substrates (regions and circuitry) through EEG and fMRI techniques (see reviews and meta-analyses: e.g., (literature

review (Baskin-Sommers and Foti, 2015); 32 studies of anhedonia in participants with substance use disorders and controls (N=48,019) (Garfield et al., 2014); 25 fMRI studies on reward processing with 643 individuals with addictive behaviors and 609 controls (Luijten et al., 2017); 22 task-based fMRI studies with adolescents vulnerable to substance use (N=1092) (Tervo-Clemmens et al., 2020). Across the three areas of reward (wanting, liking and habit), those with addictions (both adolescents and adults), reliably show deficiencies in consummatory processing (wanting) and learning (habit), with dampened saliency to natural rewards but heightened saliency to drug-related cues; less often are differences between substance users and controls seen in the realm of “liking” (e.g., Baskin-Sommers & Foti, 2015).

Hyperactive cue reactivity for immediate and low-cost reinforcers, and drug reward activations (from amygdala and subcortical circuits) have corollary impacts in the decision-making processing whereby frontal areas are recruited less than subcortical regions. Typically, those with SUDs show impulsive decision making on gambling and monetary incentive delay tasks in favor of delayed discounting. This effect is heightened under drug cue conditions compared with non-drug cues. (e.g., Bickel et al., 2011; Hulvershorn et al., 2015). Taken together, extensive research has implicated dampened saliency of natural rewards and heightened reward processing of drug-related cues in SUDs.

Reward Functioning in PTSD+SUD

Research on early life adversity or stress suggests a trajectory of adverse outcomes among those with exposure to stressors in early childhood, which include higher rates of lifetime substance initiation and use disorders (Dube et al., 2002; Penza et al., 2003). Recent conceptualizations of early life adversity/stress include reward functioning as one mechanism that may provide a bridge for understanding pathways from traumatic stress exposure and PTSD

to SUDs. Kumar et al. (2014) suggest that functional differences by type of stress (adversity versus acute stress) may be important to consider in study design (Boecker et al., 2014). Deficits in reward processing in adolescents and adults with histories of childhood adversity have generally been shown to involve hypoactive motivation and learning (e.g. Dillon et al., 2009), and hypoactivation during reward anticipation and hyperresponsiveness when receiving a reward (Boecker et al., 2014). In acute stress, the reverse is found: hypoactivation during reward anticipation but decreased responsivity on receiving reward. Reward dysfunction is therefore hypothesized to be a potent mechanism by which early childhood abuse may lead to addictions, warranting further translational study.

In adulthood, Elman and Borsook (2019) have proposed a chronic stress (“anti-reward”) and reward deficiency model for PTSD+SUD, which positions reward deficits as one of the shared neurobiological underpinnings at the core of both PTSD and SUD, conceptualizing it as a “failing cascade”. In their proposed model, independent, interactive and common developmental processes across both disorders (see Figure 2, from Elman & Borsook, 2019) initially and independently lead to reward system dysfunction, resulting in overactive sensitivity to drug rewards for substance use and dampened sensitivity to rewards with trauma exposure. Over time, however, changes in each set of disorders lead to neuroadaptations (described above) in the direction of hypo-activity of the reward system for *both* SUDs and PTSDs, which may manifest in *both* conditions in emotional numbing and anhedonia. In this view (also identified by Baskin-Sommers & Foti, 2015 and Enman et al., 2014), the *interactive* nature of the stress and reward systems leads to cyclical and reciprocally reinforcing cross-sensitization. “The sensitized stress responses in PTSD may thus confer greater motivational salience to opioid-related cues, whereas opioid consumption causes more stress and additional worsening of PTSD symptoms manifested

in the ‘spiraling distress cycle’” (Elman and Borsook, 2019). Here, associative learning processes across the two sets of conditions also become maladaptive (shared factors). To be sure, there are non-overlapping areas that may not have direct parallels across conditions, e.g., a triggering traumatic event in PTSD or struggles with craving and drug seeking behavior in SUD. To date, beyond the developmental research, there are yet to be studies in PTSD+SUD populations compared to PTSD- and SUD-only populations, using translational methods to evaluate the model proposed above, although efforts to do so will have high potential to guide novel new directions for clinical intervention. However, extant theoretical and empirical work implicates that both PTSD and SUD have reward processing deficits that may synergistically sensitize drug rewards and attenuate trauma rewards to propagate the interactive and mutually exacerbating effect of both disorders.

Domain 4: Social Cognition

Overview

Social functioning and support have been extensively studied in both PTSD and SUD and heavily implicated as risk, maintenance, and recovery factors of traumatic stress and addiction (see Brewin, Andrews & Valentine, (2000) for social support; Rupp et al. (2017) & Le Berre (2019) for substance use). Correspondingly, *social systems*, which includes how people process, store, and apply information about other people and social situations, is one of the six RDoC matrix domains. Accordingly, a fourth and final area of neurofunctional interest is *social cognition*. We note that social cognition shares the social edge of the three other neurofunctional domains (social attention/cognition, negative emotionality, and reward). Experimental research on this domain remains relatively small in PTSD (Plana et al., 2014; Sharp et al., 2012; Stevens

and Jovanovic, 2019) and in SUD (Le Berre, 2019; Ramey & Regier, 2018; Rupp et al., 2017), and non-existent for PTSD+SUD.

Social Cognition in PTSD

Three reviews have found support for deficits in types of social cognition in PTSD (Plana et al., 2014; Sharp et al., 2012; Stevens and Jovanovic, 2019). These deficits include: 1. an impaired capacity in PTSD to accurately recognize emotions and traits (i.e., trustworthiness) of others; 2. an impaired ability in PTSD to take the perspective of others or reflect on their own mental states (i.e., “mentalize”) (Sharp et al., 2012; Stevens and Jovanovic, 2019); and 3. greater threat reactivity in PTSD to social (e.g., faces) relative to nonsocial (i.e., snakes) stimuli (Stevens and Jovanovic, 2019).

Two recent studies have examined facial perceptions of fearfulness and trustworthiness in individuals with PTSD features. Fertuck et al. (2016) compared a PTSD, trauma-exposed without PTSD, and healthy control group. The PTSD group was biased to perceive faces as more *trustworthy* compared to the trauma-exposed healthy controls, yet there were no differences between groups in fear processing. A trustworthiness bias in PTSD may represent a vulnerability factor (Fertuck et al., 2016). Saraiya et al. (2019) examined PTSD features in a community sample. They found that those with higher PTSD symptoms appraised faces as more *untrustworthy* than a healthy control group. EEG data revealed an early attentional avoidance in the high PTSD group of faces morphed on dimensions of trustworthiness, which the authors interpreted as a neural mechanism of atypical processing of affiliative behavior in PTSD. The reasons for the contradictory results between the two studies are unclear. Some possibilities include: 1. different sample characteristics (i.e., Fertuck et al. (2016) utilized a clinical PTSD sample, Saraiya et al. (2019) a non-clinical one); 2. only Fertuck et al. (2016) accounted for co-

occurring conditions (e.g., Borderline Personality Disorder) associated with a bias to mistrust others (Fertuck et al., 2019, 2018, 2013; Miano et al., 2013); and 3. task modifications (Saraiya et al. [2019] appraised trustworthiness differently from Fertuck et al. (2016). Nevertheless, the two studies point to a promising avenue of processing differences in social cognition between PTSD and controls. In sum, although it remains unclear whether PTSD is characterized by a bias to perceive others as trustworthy, untrustworthy, or neither, studies suggest that PTSD is associated with problems interpreting other's internal states.

Social cognition in SUD

The literature on social cognition in SUD is emerging, and three impaired types of social cognition have been identified: 1) emotion recognition (accurately decoding the emotions of others) and alexithymia (difficulty in identifying one's own emotions), 2) insight into one's SUD, and 3) mentalization, or, theory of mind ((Le Berre, 2019; Ramey & Regier, 2018). In a systematic review, alexithymia was particularly associated with severity of alcohol misuse when considered in the context of alcohol expectancy, motives for alcohol use, urges to drink, and other co-occurring psychopathology, such as mood disorder and early adversity (Cruise and Becerra, 2018; Le Berre, 2019). In a study of individuals with AUD (Rupp et al., 2017), participants with impaired emotion recognition had greater treatment non-completion than participants with intact emotion recognition. Emotion recognition may be an important target for intervention and treatment compliance. The degree to which one has insight is a key component of substance recovery, and is impaired prior to treatment. The evidence for lack of insight into SUD, however, is mostly indirect. For instance, only 5% of those with an SUD perceive the need for treatment (Ramey and Regier, 2019). Finally, deficits in theory of mind or mentalization (for both emotions and cognitions) have been documented in AUD in particular

(Bora and Zorlu, 2017; Le Berre, 2019; Onuoha et al., 2016). Brain correlates of SUD include atypical structural and functional connectivity in amygdala, prefrontal, insular cortex, and temporal regions (Le Berre, 2019), all of which are consistent with social cognitive deficits in SUD. Nevertheless, combined social cognition and neuroimaging studies are lacking. These preliminary works suggest that the capacity to interpret and understand other's internal states may be impaired in SUD.

Social Cognition and PTSD+SUD

The degree to which social cognition impairments are a process *shared* by PTSD and SUDs has not been investigated. However, there are compelling reasons to expand research in this area. PTSD+SUD may have atypical social cognitive processing, leading to impaired decision-making in relationship choice, poor treatment adherence, and relapse, as well as severe incapacities in social and occupational adaptation.

Treatment Implications and Future Directions Across the Four Neurofunctional Domains for PTSD+SUD

Executive Function

The comprehensive body of research on executive functioning, negative emotionality, reward processing, and social cognition in PTSD and SUD has several clinical implications. As we have seen, deficits in EF processes function as either precursors or consequences of both PTSD and SUD. They may thus serve to influence the course of traditional cognitive-behavioral treatments (i.e., as predictors) or may serve as outcome variables that are amenable to treatment interventions. Studies examining the EF domain indicate that individuals with poor executive functioning, such as those with PTSD, SUD, or both, may be particularly amenable to paradigms that promote EF, and hence may serve to enhance attentional control, decision making, and

inhibitory control, and reduce attention bias (which is also part of the reward system), highlighting the plasticity of these processes (Aupperle et al., 2012; Clark et al., 2003; Harrington et al., 2012; Leskin and White, 2007; Verdejo-Garcia, 2016). For example, in an fMRI investigation of working memory, Dolcos and McCarthy (2006) found that increased activity in the ventrolateral prefrontal cortex was inversely correlated with participants' rated distractibility of threatening (but not non-threatening) IAPS images. Training threat avoidance in these tasks has therefore been suggested as a possible therapeutic treatment of anxiety disorders. Schmidt, Richey, Buckner et al. (2009), for example, trained participants with social anxiety disorder to avert threatening cues during performance of the dot-probe paradigm. The attention bias modification training led to a significant decrease in social phobia and anxiety scores relative to a placebo control, an improvement that was maintained over a 5-month follow-up. While results probing attention control training (ACT; enhances general attention in the context of threatening stimuli) and attention bias modification (ABM; training to shift attention away from threatening stimuli towards neutral stimuli) among those with PTSD have been mixed (Badura-Brack et al., 2015; Kuckertz et al., 2014; Schoorl et al., 2013), likely as a function of the varied attentional biases at play (Lazarov et al., 2019), emerging studies highlight the need for personalized treatments based on pre-treatment attention bias assessment. For example, Lazarov and colleagues (2019) randomized 50 individuals with PTSD to either ACT or ABM with the ABM intervention tailored towards the direction of the individual's pre-treatment attentional bias (i.e., bias-contingent ABM paradigm). The results showed that ACT was superior to AMB in reducing PTSD and depression symptom severity; nevertheless, bias-contingent ABM was successful in reducing attention-bias in the intended direction (Lazarov et al., 2019).

Among those with SUD, a recent review of studies of cognitive training interventions aimed at modifying attention bias, improving response inhibition, working memory, and goal-oriented training, revealed significant improvement in these cognitive processes (Verdejo-Garcia, 2016). Other systematic reviews of ABM paradigms revealed that single sessions failed to reveal positive clinical benefits on substance use outcomes (Christiansen et al., 2015; Mogoşe et al., 2014), whereas multiple sessions of ABM, particularly when implemented in participants' home environment and utilizing mobile devices, showed promise among tobacco and alcohol users (Christiansen et al., 2015). ABM paradigms thus may be combined with traditional relapse prevention therapy to reduce further substance use and risk of relapse (Kerst and Waters, 2014; McGeary et al., 2014). However, other reviews highlight that the efficacy of ABM programs for substances other than alcohol is not yet well established (Verdejo-Garcia et al., 2019). Moreover, SUD researchers have suggested that the ABM interventions are highly intensive and demand significant cognitive resources, limiting their real-world utility. Therefore, they suggest that strategically combining intervention models to target multiple neuropsychological domains at once and focusing on ways to translate these models to real-world settings may optimize treatment outcomes for SUD (Verdejo-Garcia et al., 2019).

Overall, findings suggest both global executive function training and specialized ACT and ABM paradigms serve as potential useful adjuncts or alternatives to traditional cognitive-behavioral treatments for PTSD, SUD, and PTSD+SUD. Unfortunately, many extant studies were plagued by small sample sizes and conducted using laboratory-based intervention paradigms; thus, it remains to be seen whether some of these findings are transferrable to "real-life" clinical contexts. As highlighted by Verdejo-Garcia and colleagues (2019), more randomized controlled trials with individuals with PTSD+SUD are needed in order to understand

the role of executive functions as moderators and mechanisms of PTSD+SUD treatment outcomes.

Negative Emotionality

Evidence of shared disruptions in the stress response and regulation of negative emotions suggest that therapeutic approaches that enhance emotion and stress regulation may be particularly suitable for PTSD+SUD populations. Trauma-focused protocols such as Skills Training in Affect and Interpersonal Regulation (STAIR), Dialectical Behaviour Therapy (DBT) with DBT-Prolonged Exposure (Harned et al., 2014), which center on the acquisition of emotion regulation skills, could be adapted to address clinical issues specific to PTSD+SUD patients. To date, STAIR, DBT+DBT PE—or any other emotion regulation therapy—has not been tested with this comorbidity. The centrality of dysregulated fear in PTSD also points to the importance of trauma-processing therapies in which conditioned responses to traumatic memories may be modified (Concurrent Treatment for PTSD and SUD with Prolonged Exposure (COPE), (Back et al., 2014).

One emergent treatment area involves the combination of behavioral exposure approaches with medications that may augment the extinction learning process (e.g. d-cycloserine (Rothbaum et al., 2014), yohimbine (Tuerk et al., 2018), dexamethasone [Surís et al., 2017]). Another promising pharmacotherapy approach is the targeting of receptors that modulate stress. In animal studies, selective serotonin reuptake inhibitors have been shown to reduce stress-related drug self-administration (Huot et al., 2001; Lê et al., 2006); as a pharmacotherapy for PTSD+SUD, sertraline has received some support in human clinical trials (Brady et al., 2005; Hien et al., 2015). When PTSD+SUD is considered from the perspective of gene-environment

interaction, future treatment strategies may capitalize on the use of epigenetic regulators to facilitate the normalization of altered HPA axis activity (see Pizzimenti & Lattal, 2015).

Improvements in distress tolerance may also be a mechanism through which PTSD and SUD treatments work. Several studies show that higher distress tolerance at baseline (e.g., on the PASAT), and improvements in distress tolerance during treatments, predict better PTSD and/or SUD treatment outcomes (e.g., Banducci et al., 2017; Hasan et al., 2015; Levy et al., 2018; Reese et al., 2019). Lower distress tolerance on the PASAT also predict shorter periods of time in SUD treatment (Tull et al., 2013) and early treatment drop out (Daughters et al., 2005). These findings collectively suggest that targeting distress tolerance may improve PTSD and SUD treatment outcomes and retain individuals in SUD treatments.

Reward Functioning

Dysfunctional aspects of reward processing provide a transdiagnostic bridge for understanding shared mechanisms between PTSD and SUD that ultimately bear on existing and new directions for clinical intervention (e.g., Vujanovic et al., 2017). In adolescence, hyperactivity of reward processing and decision-making impacts the development of substance use, misuse and disorders, and often co-occurs with related conditions like ADHD. Adjunctive approaches that can draw upon community reinforcement techniques to provide incentives for prosocial behavior and abstinence (Murphy et al., 2012), contingency management, and behavioral activation would ameliorate reward dysfunction and enhance the saliency of rewards other than substance of abuse.

PTSD and SUD treatments that target the reward system can also address the common anhedonic symptoms such as affective numbing, social withdrawal, and foreshortened sense of future. One recent clinical trial combined motivational incentives with prolonged exposure

(Schacht et al., 2017); rewarding session attendance and treatment completion yielded positive outcomes in both PTSD and SUD symptoms. Yet despite the need to improve treatment attendance and dose-related outcomes, many of the current clinical behavioral interventions that emphasize coping skills building and psychoeducation about PTSD+SUD do not provide key techniques or applications to address reward deficits directly. Efforts to combine behavioral and psychopharmacologic (e.g., SSRIs) approaches encourage treatment advances that more directly target reward-related deficits for those with PTSD+SUD. In the translational area, pre-treatment measures to identify those with specific reward-related dysfunctions prior to active intervention or medication will serve to enhance treatment matching. Clearly, this review of reward deficits in PTSD+SUD provides new avenues for future treatment development.

Social Cognition

Social cognitive constructs, in particular alexithymia (Cruise and Becerra, 2018; Le Berre, 2019), emotion recognition (Le Berre, 2019), theory of mind (Sharp et al., 2012), awareness of illness (Ramey & Regier, 2018) and trustworthiness appraisal (Fertuck et al., 2016; Saraiya et al., 2019) have been implicated as developmental risk factors, core deficits, treatment mediators (Ramey and Regier, 2019) and intervention targets in PTSD and SUD (Le Berre, 2019; Onuoha et al., 2016). However studies of these promising constructs are lacking in PTSD+SUD. Developmentally, childhood adversity and early trauma likely transact with genetic and personality traits to shape divergent trajectories of both PTSD, SUD, or their co-occurrence. Social cognitive impairment may also serve as a mediator of the influence of these different trajectories. One emerging line of social cognition research involves the study of social emotions relevant to trauma, such as trust, shame, guilt. For example, critical for affiliation and

attachment is the ability to accurately decide who is trustworthy and, in the face of new information, to adjust judgments of others' trustworthiness accurately, flexibly, and efficiently. For PTSD+SUD, interpersonal trust, reactivity to social threat, and other interpersonal difficulties involving social cognition (affective and cognitive mentalizing) may be crucial yet heretofore understudied targets for treatment development in order to obtain impactful, stable therapeutic change. While extant treatments have focused primarily on trauma processing and skill-building for PTSD+SUD (Back et al., 2015; Hien et al., 2015), treatment developers might incorporate social decision making around predicting and avoiding potentially traumatic situations and persons. Further, mentalization-based treatments specifically targeting deficits in self-awareness and emotion recognition may be adapted to PTSD+SUD, particularly for those who not respond to other established interventions. Accordingly, improving social cognition may be helpful to reduce recidivism and relapse.

Taken together, these bodies of research highlight innovative and exciting new lines of inquiry for PTSD+SUD treatment. Indeed, infusing PTSD+SUD treatments with executive functioning paradigms, emotion regulation training, reinforcement paradigms such as contingency management and behavioral activation, and promoting theory of mind, may all enhance outcomes. Crucial in the exploration of these avenues is identifying when and for whom such adjunctive interventions may be beneficial.

Recommendations for Future Study

None of the four neurofunctional domains exists in a vacuum. Rather, they are embedded within and intersect with key contextual variables that alter them and their relationship to PTSD+SUD. Individual, interpersonal, and systemic factors must be considered and expanded in future studies within the neurofunctional domains discussed here. We present these

neurofunctional domains as starting points for research, assessment, and treatment and, as such, must be informed and further adapted by future systematic study.

Furthermore, we have drawn broadly upon a developmental, phased model for considering the etiology and relationships between the development of posttraumatic stress disorders in relation to development of SUD. Such a temporal model suggest that there may be variations in how and when relationships between alterations in any one of the domains may impact the unfolding of difficulties in another domain. See Figure 3 for a display of common pathways between PTSD+SUD. For example, EF deficits may be a risk factor that precedes both trauma exposure/PTSD and the subsequent development of substance use, whereas negative emotionality may be a consequence of trauma exposure. Or EF and negative emotionality changes may be more relevant in different stages of PTSD. And substance use may emerge as a means of addressing the negative emotionality in PTSD. Social cognition may be risk factor, but also a consequence of trauma. It will be important for future research to consider the temporality in relationships across these four domains as they pertain to both PTSD and SUD.

Embracing the AARDoC model enables us to characterize treatment outcomes more broadly, and within a larger transdiagnostic frame. Calls in the field for treatment approaches that are “patient centered” (i.e., Patient Centered Outcomes Research) and allow for outcomes that emphasize metrics like quality of life and individually specific change can draw from our unifying translational framework, as well as provide new ways to consider treatment mechanisms.

The contemporary gold-standard approach to intervention research is to elucidate the mechanisms of disorders such as PTSD+SUD, assess those mechanisms, and demonstrate that normalization of these mechanisms is associated with particular treatment models (Kazdin,

2007). In order to advance the field of PTSD+SUD diagnosis and treatment, we believe we must: 1) test theorized potential mechanisms of action at multiple units of analysis, from behavioral to neurobiological, and 2) discern how relationships among mechanisms account for outcomes in PTSD+SUD symptoms, as well as multiple neurofunctional domains. Future studies must also work to overcome limitations in the extant literature, including a lack of animal models and inconsistencies in methodologies and measurement. Furthermore, there is considerable overlap between key neurobiological domains, such as negative emotionality and social cognition, executive functioning and emotion regulation, and reward pathways and negative emotion. Considerably more research is required to disentangle these overlaps and identify whether fewer core deficits permeate across these domains.

Conclusion

While a number of theoretical models have documented a complex conceptualization of both PTSD and SUD—characterized by underlying psychological mechanisms and neurobiological substrates—few studies have been able to empirically examine these key elements in clinical trials for PTSD+SUD. This is particularly striking because, across the four neurofunctional domains, a body of separate experimental findings already exists. Additionally, clinical trials reveal that integrated approaches to PTSD+SUD treatment – that is, combining coping skills, fear habituation, and cognitive restructuring in cognitive behavioral therapy – reduce symptom severity in both PTSD and SUD (see e.g., meta-analyses including Hoffman et al., (2018); Simpson & Petrakis, (2017), Roberts, Roberts, Jones & Bisson (2015). However, because few studies have examined outcomes beyond symptom reduction, or mechanisms of action, little is known about how shared PTSD+SUD mechanisms impact or are impacted by preventive and treatment interventions. Currently, the absence of such research consequently

obstructs the development of tailored and optimally efficacious intervention efforts. In response, our review aimed to synthesize a disparate, but innovative series of literatures regarding the core neurofunctional alterations that underpin PTSD, SUD, and their co-occurrence. Our overarching goal was to identify the overlapping neurofunctional systems at play in PTSD+SUD, which could be used to personalize and optimize interventions for this highly prevalent comorbidity. Building upon the AARDoC framework, we reviewed four domains that comprise a unifying translational framework for studying PTSD+SUD, and an agenda for future research directions in these fields: executive function, negative emotionality, reward, and social cognition. Research clearly implicated all of these domains in both disorders, and potentially their co-occurrence. Translational clinical implications of experimental findings in each of the domains were presented as was guidance on future directions. Not only have we provided a framework to improve our methodologies for understanding how and for whom validated PTSD+SUD treatments work, we have argued that having such a framework will also enable us to identify mechanisms and characterize the PTSD+SUD comorbidity at the level of the *individual patient*, which in turn enhances treatment matching and further serves to advance novel treatment development and innovations.

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