Diminished positive affect and traumatic stress: A biobehavioral review and commentary on trauma affective neuroscience

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ABSTRACT

Post-traumatic stress manifests in disturbed affect and emotion, including exaggerated severity and frequency of negative valence emotions, e.g., fear, anxiety, anger, shame, and guilt. However, another core feature of common post-trauma psychopathologies, i.e. post-traumatic stress disorder (PTSD) and major depression, is diminished positive affect, or reduced frequency and intensity of positive emotions and affective states such as happiness, joy, love, interest, and desire/capacity for interpersonal affiliation. There remains a stark imbalance in the degree to which the neuroscience of each affective domain has been probed and characterized in PTSD, with our knowledge of post-trauma diminished positive affect remaining comparatively underdeveloped. This remains a prominent barrier to realizing the clinical breakthroughs likely to be afforded by the increasing availability of neuroscience assessment and intervention tools. In this review and commentary, the author summarizes the modest extant neuroimaging literature that has probed diminished positive affect in PTSD using reward processing behavioral paradigms, first briefly reviewing and outlining the neurocircuitry implicated in reward and positive emotion and its interrelationship with negative emotion and negative valence circuitry. Specific research guidelines are then offered to best and most efficiently develop the knowledge base in this area in a way that is clinically translatable and will exert a positive impact on routine clinical care. The author concludes with the prediction that the development of an integrated, bivalent theoretical and predictive model of how trauma impacts affective neurocircuitry to promote post-trauma psychopathology will ultimately lead to breakthroughs in how trauma treatments are conceptualized mechanistically and developed pragmatically.

1. Introduction

Close to 80% of individuals will experience a traumatic event over the course of life (Stein et al., 1997), which has been defined diagnostically as either direct or vicarious exposure to actual or threatened death, serious injury, or sexual assault, or learning about such an event happening to a close significant other (APA, 2013). As a result of experiencing a trauma, most individuals will experience some form of psychiatric symptomatology that typically resolves within days following the experience (Yehuda and LeDoux, 2007). However, a significant minority of individuals fail to display the normal course of recovery and go on to manifest a form of post-trauma psychopathology, which most frequently manifests as post-traumatic stress disorder (PTSD) (O'Donnell et al., 2004). PTSD has an enormous public health burden by virtue of its high prevalence (Kessler et al., 1995),

persistence (Kessler et al., 2017), accompanying functional impairment (Norman et al., 2007), and elevated risk of other mental (Flory and Yehuda, 2015; Walton et al., 2018) and physical disorders (Krakow et al., 2015; Neigh and Ali, 2016).

PTSD is characterized by predominant symptoms of intrusive re-experiencing of the traumatic event (e.g., thoughts, images, dreams), avoidance of trauma-related internal (e.g., thoughts) and external stimuli (e.g., people, places, and situations), symptoms of hyperarousal and exaggerated reactivity to threat, and a cluster of symptoms that has classically been termed "emotional numbing" (Litz and Gray, 2002) characterized by emotional response deficits such as restricted range of affect (e.g., unable to have loving feelings), feelings of detachment or estrangement from others, and markedly diminished interest or participation in significant activities (APA, 2000). The restricted range of affect criterion was most commonly thought (Litz and Gray, 2002) and

empirically found (Kashdan et al., 2006; Litz et al., 2000) to reflect a deficit in the ability to experience positive emotions, which is closely related to the transdiagnostic psychiatric construct of anhedonia—the inability to experience pleasure and a general lack of reactivity to and pursuit of ostensibly pleasurable stimuli. Though the manifestations of anhedonia are varied and have been proposed to reflect several unique domains of behavior and experience (Treadway and Zald, 2011), all are characterized by an absence of some capacity involved in obtaining and/or sustaining pleasurable experiences and emotional states. The most recently updated diagnostic system has thus clarified this restricted range of affect criterion in PTSD to focus specifically on inability to experience positive emotions (e.g., happiness, satisfaction, or loving feelings), which reflects the most commonly reported emotional deficit in individuals with PTSD: diminished positive affect. This stands in stark contrast to the frequently reported exaggerated manifestation of other emotions including fear, anger, and disgust (Finucane et al., 2012). Positive affect can be defined as the frequency and intensity with which an individual experiences positive valence emotion and its associated response tendencies, e.g. happiness, joy, interest, desire/capacity for interpersonal affiliation, motivation, humor, and subjective well-being (Miller, 2011), and these experiences are predominantly reduced both in intensity and frequency in individuals suffering from PTSD (Kashdan et al., 2006).

Although these deficits in positive affect are profound, they are a historically understudied aspect of trauma symptomatology both from a treatment development and biomechanistic perspective. A large portion of early trauma neuroscience research efforts focused on elucidating the neurocircuitry involved in the acquisition, maintenance, and expression of heightened fear and threat responses that are also prominent manifestations of post-traumatic stress, using techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), with later research efforts expanding to include related constructs of interest such as cognitive function, cognition-emotion interactions, and social cognition (Liberzon and Sripada, 2008). The relative inattention to systematic study of the biobehavioral processes underlying diminished positive affect is particularly detrimental to the advancement of the field given that higher levels of diminished positive affect symptoms in PTSD are associated with a plethora of poor clinical outcomes, including greater distress and disorder chronicity (Breslau et al., 2005; North et al., 2009), greater degree of functional impairment (Hassija et al., 2012; Norman et al., 2007), poorer outcomes to psychotherapy (Taylor et al., 2001), and increased suicidality (Guerra et al., 2011). Moreover, the diminished positive affect observed in PTSD is present both with and without comorbid major depressive disorder (Franklin and Zimmerman, 2001), and alterations in positive emotion represent diagnostic criteria for both disorders (APA, 2000, 2013). Thus, this group of PTSD symptoms is not just an artifact of diagnostic comorbidity and could represent a promising target for the development of novel intervention tools. Fortunately, over recent years increasing attention has been devoted towards the study of diminished positive affect in PTSD (Nawijn et al., 2015), particularly in the context of reward processing paradigms that probe behavioral, affective, and neurocircuitry responses to positive valence stimuli. This review focuses on briefly summarizing and highlighting relevant findings from the study of reward processing in adults with PTSD, with a primary focus on biobehavioral studies that assess neurocircuitry dynamics and biomarkers underlying post-trauma diminished positive affect.

First, the neurocircuitry involved in reward and positive emotion as elucidated by animal and human studies is briefly described and defined, and interactions between positive and negative valence brain systems as informed by experimental studies are discussed to highlight a potential mechanistic bridge from the experience of a traumatic event to the development of blunted positive affect. Then, the current state of the PTSD literature is summarized by reporting on neuroimaging and electrophysiological studies assessing brain responses to rewards and other experimental stimuli typically provoking positive emotional

responses in those with intact positive affect. Finally, the author critically analyzes the current gaps in existing knowledge in this area of study and proposes a line of research across several domains to systematically address the current positive-valence vacancy in trauma neuroscience. The overarching motivation behind this manuscript is to inform and advance—that is, inform the reader of the current state of knowledge regarding the affective neuroscience of post-trauma diminished positive affect and its relevance to clinical outcomes and treatment development, and to advance the study of this domain to one of higher priority in the field of trauma research.

2. The neurocircuitry of reward and positive emotion

2.1. The reward circuit: brief history and anatomy

Animal and human studies have repeatedly verified the role of an interconnected group of neuroanatomical structures in the anticipation, pursuit, and consumption of rewarding stimuli (for an excellent review, see (Haber and Knutson, 2010)), and these same structures are also implicated in the experience of positive emotion and positive affect in humans (e.g. (Mobbs et al., 2003),). This canonical "reward circuit" encompasses regions of the midbrain, striatum, and orbital and medial prefrontal cortex, and it is heavily implicated in nearly all temporal phases and modalities of reward processing (Sescousse et al., 2013), while a more extended neurocircuitry outside of this canonical reward circuit is also heavily implicated in related processes supporting reward and pleasure (Berridge and Kringelbach, 2015). The characterization of this circuit began with studies in rats over half a century ago assessing motivation to "work" for the ability to stimulate electrodes placed into specific brain structures (Olds and Milner, 1954), which were later identified to be active sites of stimulation by drugs of abuse (McBride et al., 1999). These sites of self-stimulation include the ventral tegmental area (VTA) of the midbrain and the nucleus accumbens and surrounding regions of the ventral striatum and ventral pallidum (Haber and Knutson, 2010). These sites, in particular, form an interconnected network of "hedonic hotspots" that can be causally modulated by experimenters with electrical stimulation in order to selectively enhance "liking" reactions of animal subjects, although additional stimulation sites that could serve a similar brain function of enhancing pleasure reactions have also been identified in the brainstem (parabrachial nucleus of the pons), as well as the orbitofrontal cortex and insula (Berridge and Kringelbach, 2015).

2.2. "Liking" vs. "wanting" in the reward circuit: neurotransmitters and circuit characteristics

Recent work in the reward processing field has emphasized the distinction between "liking", i.e. the subjective pleasurable experience of some stimulus, vs. "wanting", i.e. the drive or "felt" motivation to obtain some rewarding or pleasurable stimulus or experience, also termed "incentive salience" (Berridge and Kringelbach, 2015; Kringelbach and Berridge, 2009; Treadway and Zald, 2011). These two constructs are easily dissociable in the case of one's subjective experience (e.g., the enjoyment of eating a delicious meal is quite different from the experience of desiring one), but the neurotransmitters and functional neuroanatomy supporting their emergence in organismic awareness also diverge to an extent. Of interesting note is the fact that the identified hedonic hotspots mentioned in the prior section form only a small portion of the volume of the implicated anatomical structure, suggesting that brain regions such as the ventral striatum and ventral pallidum, although having specialized portions devoted to the experience of pleasure, are far from selectively evolved for this process. Indeed, a posterior region closely adjacent to rostrodorsal portion of the nucleus accumbens shell, a subdivision of the structure classically considered to be the seat of pleasure in the brain, is known to be a "hedonic coldspot", such that neurochemical stimulation of this region
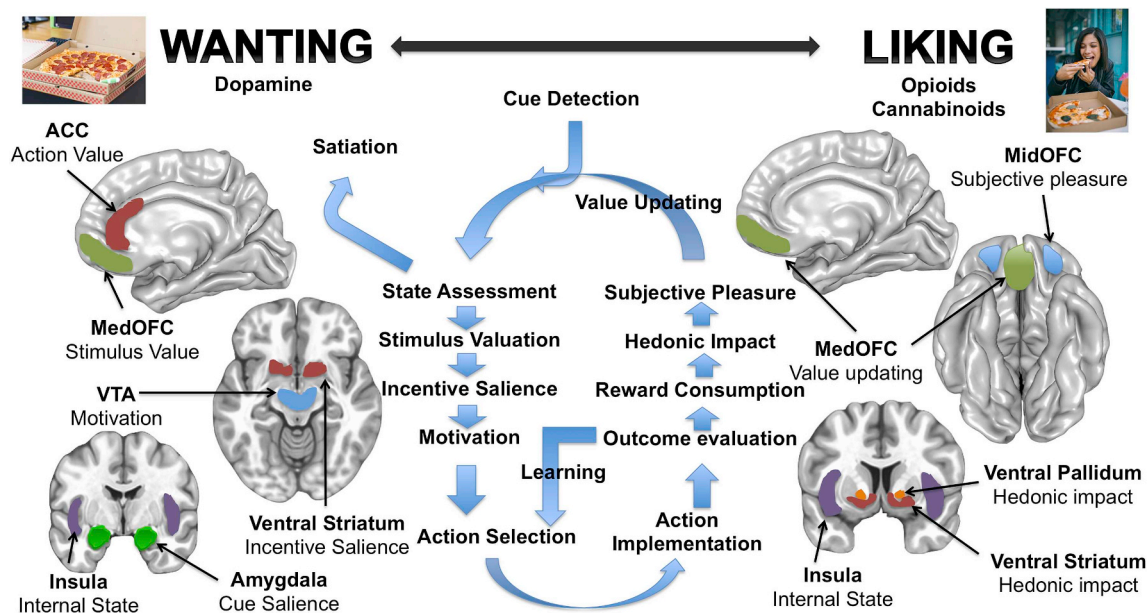
Fig. 1. "Wanting" and "Liking": Circuitry and Constructs of A Cyclical Process"
This figure depicts a simplified heuristic for the circuitry and constructs involved in the reward seeking and consumption cycle. On the left side of the figure is depicted the circuitry and constructs mostly closely related to "wanting" and reward seeking (which rely on the neurotransmitter dopamine), while on the right side are the circuitry and constructs most closely related to "liking" and reward consumption (which rely on opioid and cannabinoid neurotransmitter systems). Note there is no clear demarcation between these two interrelated processes, and they exist on a continuum of reward-related behaviors (represented by the double-sided arrow). The brain pictures illustrate the circuitry and constructs involved in different aspects of reward processing (with those on the left pertaining to "wanting" and those on the right to "liking"), while the cycle in the center represents the cyclical relationship between them. When a reward-predictive cue (e.g., the sight of a pizza) is detected (upper left corner), the salience of the cue is signaled by the amygdala. The cue salience is then integrated with homeostatic information regarding the organism's internal state (i.e. degree of hunger) in the insula, and the cumulative expected value of the reward predicted by the stimulus (stimulus value) is computed in the medial orbitofrontal cortex (medOFC). The incentive salience of the cue is signaled by the ventral striatum and the motivation to obtain the reward is signaled by dopaminergic neurons originating in the ventral tegmental area (VTA). The relative value of the actions (action value) needed to obtain the reward (e.g., get in line, pay money) is represented in the anterior cingulate. Actions are then selected and implemented, and outcomes are evaluated for success. When outcomes are unexpected (e.g., no money in wallet), learning occurs (via prediction error signaling in the ventral tegmental area and ventral striatum), action values are updated, and actions are re-implemented (e.g., ask a friend for money). When the reward is attained, consumption occurs (e.g., eating the pizza, upper right corner). The hedonic impact of the reward is computed in the ventral striatum and ventral pallidum, which is combined with internal state information from the insula to result in a representation of the subjective pleasure of the rewarding experience in the mid-anterior orbitofrontal cortex (midOFC). The subsequent reward value of the stimulus is then updated in the medOFC. As satiation occurs, the reward predictive cue (sight/smell of pizza) when combined with the organism's internal state assessment engenders less of an incentive salience signal, and as the subjective value of the reward diminishes the cycle of reward seeking and consumption ceases.

will suppress liking responses in animals but still motivate behaviors to obtain rewards, i.e. "wanting" (Berridge and Kringelbach, 2015). Thus, these two reward processes of "liking" and "wanting" have shared and distinct neurocircuitry and neurochemical messengers yet are inextricably related through the way in which each process reciprocally influences the other (see Fig. 1). Specifically, the hedonic pleasure or "liking" of some stimulus (e.g., eating a delicious meal) reflects the sum total of one's exteroceptive and interoceptive input at that moment combined (e.g., physiological state, degree of satiety, etc.) with the subjective value attributed to that experience, which can serve to reinforce and condition motivated behavior towards future effort expenditure in obtaining that stimulus again. This subjective "liking" of a stimulus, as revealed by imaging studies, appears to be coded in the brain in mid-anterior and medial regions of the orbitofrontal cortex, ventromedial prefrontal cortex, anterior cingulate, as well subcortically in the ventral striatum and ventral pallidum (Kringelbach and Berridge, 2009). Thereafter, the incentive salience attributed to some reward-predictive cue (e.g., the smell of food), which itself is partially dependent both on past experience as well as the current physiological state of the organism, will trigger a motivational state that is experienced as "wanting" a rewarding stimulus as well as the engagement of behavior necessary for its obtainment and the subsequent consumption of the pleasurable experience it affords (Berridge, 2007; Smith et al., 2011). Such behaviors, in uncertain environments, may need to be deployed and adjusted based on trial and error learning until the desired outcome

is attained. This process of "wanting" also appears to recruit the nucleus accumbens/ventral striatum as well as diverse regions of the prefrontal cortex (Berridge and Kringelbach, 2015), while the process of trial and error learning additionally recruits the midbrain, likely encompassing the ventral tegmental area (Chase et al., 2015). The midbrain is additionally recruited during internal volitional attempts to engage a motivational state in the absence of any rewarding cue or feedback (MacInnes et al., 2016).

The neurochemicals known to augment these separable yet related processes are distinct, yet they share overlapping targets on implicated neural substrates, particularly in regions of the ventral striatum and ventral pallidum. "Liking" reactions are selectively enhanced by mu, kappa, or delta opioid receptor agonism in the nucleus accumbens hedonic hotspot (Smith et al., 2009), and stimulation of endocannabinoid receptors in this same region also produces a similar enhancement of "liking" reactions (Mahler et al., 2007). Thus, drugs of abuse such as opiates and cannabis exert neurochemical effects on neuroanatomical brain targets that are optimally situated to promote feelings of pleasure and happiness, which no doubt contribute to susceptibility to escalating use (Koob and Volkow, 2016). Additionally, agonism of receptors for gamma amino butyric acid (GABA), the brain's primary inhibitory neurotransmitter, in the nucleus accumbens hedonic hotspot also enhances "liking" reactions. However, this enhancement is thought to occur via a different mechanism than that of opioid or endocannabinoid receptor activation, as GABA agonism promotes neuronal

hyperpolarization and decreases firing rate. As neurons in the nucleus accumbens projecting back to the ventral tegmental area (VTA) and ventral pallidum are themselves inhibitory and primarily GABAergic, this GABA agonism-facilitated enhancement of "liking" may occur through inhibition of an inhibitory process, i.e. disinhibition of neuronal mechanisms governing the hedonic response (Berridge and Kringelbach, 2015). In contrast, the neurotransmitter most typically associated with reward and pleasure in popular media and pop culture, dopamine, is now thought to mediate reward-related processes distinct from that of pleasure and liking. In particular, dopamine has been proposed to be the brain's neurochemical mediator of incentive salience, i.e. the internal signal for drive or motivation to engage in behavior necessary to obtain or consume a reward (Berridge, 2007).

2.3. Decisions, decisions: learning to predict and obtain rewards through reinforcement

A crucial capacity integral to the survival of any mammalian organism is its ability to learn from past experience and use this information to guide adaptive behavior in complex environments. In cases where an animal's behavioral response to some predictive cue dictates some desirable or undesirable outcome, this capacity is often studied experimentally under the auspices of operant reinforcement learning, which examines and attempts to predict mathematically how an agent will take actions in some environment in order to obtain rewards and avoid punishments (Dayan and Balleine, 2002). Critically, such learning typically occurs through trial and error. In this framework, arising out of computer science and artificial intelligence, initial predictions for the upcoming rewards associated with some conglomerate of predictive cues (which initially have no predictive value) is successively updated through comparing outcomes received to outcomes expected, assessing the difference, and then using this comparison to update predictions (Dayan and Balleine, 2002). Dopamine has been popularly implicated (though not undisputed) in this particular reinforcement learning process for rewards (Berridge, 2007; Montague et al., 1996), specifically the coding of internal "teaching" signals known as "prediction errors". Prediction errors are a comparison of expected and received outcomes following some behavior that are used to guide learning and update internal representations of relationships between predictive stimulus, chosen behavior, and received outcome (Schultz, 2015). The reward-predictive "weights" attributed to stimuli associated with a later rewarding outcome are known as "value" estimates in a reinforcement learning framework (Dayan and Niv, 2008). Consistent with these hypotheses, one of the brain's primary dopaminergic pathways (the mesolimbic dopamine system) comprises projections from the VTA to the ventral striatum and prefrontal cortex, thus demonstrating a convergent neurochemical and neuroanatomical pathway for the instantiation of these aspects of reinforcement learning-based reward processing in reward circuitry (Haber and Behrens, 2014). Moreover, the VTA and ventral striatum, specifically, have been identified in numerous correlational computational model-based imaging studies to encode the prediction errors used to guide behavior and update internal representations of stimulus-reward contingencies, i.e. the "value" estimate attributed to some reward-predicting stimulus (D'Ardenne et al., 2008; Garrison et al., 2013). The ventral striatum, in particular, is also heavily implicated in reward anticipation (Knutson and Greer, 2008), a process which shares some similarity with the construct of value in reinforcement learning, i.e. a stimulus predicting the possibility of some upcoming or future reward, and as such has also been implicated in neuroimaging studies as representing the encoding of subjective value along with the ventromedial prefrontal cortex (Bartra et al., 2013). Importantly, however, the necessity and sufficiency of dopamine neurotransmission for facilitating learning through prediction errors has been challenged (Berridge, 2007), and it has been proposed that a more globally applicable mechanism such as prefrontal cortical glutamatergic input to

the striatum (given that glutamate is the brain's primary excitatory neurotransmitter and is critically involved in neuroplasticity, learning, and memory (Peng et al., 2011)) may be the actual mechanism of learning *per se*.

Along with the ventral striatum, regions of the ventromedial prefrontal cortex (including the anterior cingulate and medial/orbital frontal gyri) are most commonly implicated in tracking subjective reward value, or the rewarding properties of a stimulus and the actions necessary to obtain the reward (Bartra et al., 2013). Specifically, the medial orbitofrontal cortex is thought to associate stimuli with reward values, while the anterior cingulate is more heavily implicated in the association of actions with reward value (Camille et al., 2011). Thus, the anterior cingulate (both ventral and more dorsal portions) is generally implicated in the "wanting" or reward pursuit phase, in which actions to obtain rewards are implemented and assessed for their relative value (Rudebeck et al., 2008). This ventromedial prefrontal tracking of reward value encompasses an integration of both sensory and stimulus information, typically occurring in regions of the medial orbitofrontal cortex (Haber and Knutson, 2010), with a cortical representation of the hedonic value of a stimulus in the mid-anterior orbitofrontal cortex to form a unified representation of the subjective experience of reward or pleasure (Berridge and Kringelbach, 2015). Thus, the passive observation of stimulus-reward contingencies, learning, and appraisal of reward value of a stimulus are primarily encoded in the ventral regions of the canonical reward circuit, including the medial and mid-anterior orbitofrontal cortex, ventral striatum, ventral pallidum, and VTA.

2.4. Beyond the reward circuit: complementary processes

The functions of the canonical reward circuit are additionally complemented by myriad neurobehavioral processes instantiated in other brain structures that non-selectively inform and guide multiple aspects of organismic behavior, including reward. This includes more dorsal regions of the striatum, which are thought to be a site of integration for cognitive, sensory, and motivational information in choosing and implementing actions to obtain rewards (Balleine et al., 2007), as well as the dorsomedial and dorsolateral regions of the prefrontal cortex, involved in motor preparation, action selection, and higher-order cognitive processes used to guide and regulate reward-seeking behaviors (Haber and Knutson, 2010). This "reward-support" circuitry also includes the amygdala, a subcortical structure that plays a crucial role in the detection of salient environmental stimuli, both positive and negative (Costafreda et al., 2008; Kim et al., 2016a,b), as well as the mounting of subjective and physiological emotional responses (Feinstein et al., 2011). Likewise, the insular cortex, a paralimbic substrate critically involved in interoception (the sense of the overall physiological condition of the body)(Craig, 2003), integrates ascending physiological information to produce representations of the body state at a given moment in time. These physiological representations are thought to provide an internal scaffold upon which subjective experiences of emotion and affect are based (Craig, 2009). As such, these regions play a critical role in the detection of a stimulus that might serve as a reward or a reward-predicting cue and the appraisal of affective and physiological changes involved in the subjective experience of pleasure or positive emotion. Additionally, other subcortical regions, such as the medial dorsal nucleus of the thalamus, habenula, subthalamic nucleus, hypothalamus, and pedunculopontine tegmental nucleus, form either core components of the corticothalamostriatal loops comprising the brain's reward circuitry and/or regulate or inhibit the reward circuit in favor of other adaptive organismic processes (Haber and Knutson, 2010), while hippocampal and parahippocampal regions are critically implicated in memory processes crucial to learning and retrieving cue-outcome and cue-context associations (Wimmer et al., 2012).

2.5. Positive affect and positive emotion: more than just reward

The affective and emotional states experienced by humans are complex and nuanced, and this property ultimately renders them difficult to study in a laboratory setting in a way that provides generalizable information regarding the mechanisms underlying their emergence and sustenance. Consequently, positive emotion and positive affect are typically studied experimentally utilizing reward-processing paradigms, which probe positive valence brain systems but do not necessarily induce positive emotion *per se*. However, there are important distinctions between these constructs worthy of mention. Here, reward processing is meant to refer to the narrow experimental construct, which concerns itself with the whole organismic response to obtaining, consuming, or learning about a subjectively pleasing or positive valence stimulus or experience. More generally, positive emotion is meant to denote a subset of positive affective phenomena, specifically multi-component response tendencies that unfold over a relatively short period of time and typically occur in response to some antecedent event, involve some conscious or unconscious appraisal of the event, and trigger a cascade of responses including changes in subjective experience, facial expression, physiology, and cognitive processes (Fredrickson, 2001). Finally, positive affect is the most general class and pertains to pleasant consciously accessible feeling states, which may or may not have an object or event attached to them and tend to be less multi-component in their constitution (i.e. may only involve a subjective experience without associated antecedent event or physiological changes)(Fredrickson, 2001). This distinction is germane to the topic of this paper given that PTSD is likely associated with deficits in the broadest category, i.e. positive affect, which subsumes within it deficits in positive emotional experience as well as reward processing *per se*.

Attempts to elucidate the neurocircuitry underlying positive emotion more specifically have utilized experimental manipulations to induce positive emotions in participants, such as positive autobiographical memory recall (Li et al., 2016; Speer et al., 2014), self-directed induction of compassionate feelings (Engen and Singer, 2015), and presentation of humorous stimuli (Mobbs et al., 2003) or sexually explicit film clips (Greenberg et al., 2015), all of which have been found to up-regulate activation in the canonical reward circuit nodes of the ventromedial prefrontal cortex and ventral striatum. Thus, the intact functioning of these neuroanatomical structures appear to be crucial to the processing of general positive valence, from the most circumscribed context-bound stimuli (rewards and reward predictors) to more general internally or externally cued positive emotional states. However, what is furthermore apparent from these studies is the need for conjoint activation of multiple distributed cortical and subcortical networks in eliciting and sustaining positive emotion in conjunction with the reward circuit proper, including higher-order associative cortices contained within dorsal and lateral prefrontal cortical regions, posterior parietal cortex, temporal poles, and posterior lateral temporal structures, as well as phylogenetically older brain structures such as the dorsal striatum, insula, amygdala, hypothalamus, and the cerebellum. The involvement of these distributed structures in positive emotional experience, which are not considered to be part of the canonical reward circuit, is consistent with the conceptualization of emotions as temporally distinct multicomponent response tendencies that involve an antecedent event, an appraisal, and a conglomerate of subjective and physiological responses (Fredrickson, 2001). Thus, an intact capacity to subjectively experience positive emotion, which is a core phenomenology of the self-reported clinical deficit underlying diminished positive affect in PTSD and major depression, likely necessitates and recruits a multitude of distributed brain regions including the canonical reward circuit, but not limited to it. Indeed, positive affect induction work in major depression has demonstrated that individuals with the disorder display an impaired ability to sustain activation in the nucleus accumbens when deliberately attempting to up-regulate positive emotion

to an emotion-inducing picture, and this deficit relates to self-reported experience of positive emotion. Likewise, functional connectivity (a measure of coherence of function across time in two or more brain structures during a behavior) between the nucleus accumbens and the dorsolateral prefrontal cortex was likewise impaired in the depressed patients, suggesting that deficits in positive emotion reflect an inability to utilize prefrontal resources to modulate core reward-related ventral striatal processes (Heller et al., 2009). Interestingly, a greater degree of improvement in positive affect following antidepressant treatment was associated with a greater degree of remediation of these circuit deficits (Heller et al., 2013). Though no comparable positive emotion amplification imaging work has yet been conducted in PTSD, these findings suggest that trauma-induced deficits in the ability to experience and sustain positive emotions may reflect not only a disturbance within the striatal portions of the reward circuit but also the capacity to integrate the information processed therein with that of more widely distributed brain structures.

3. The positive and negative valence interplay: stress effects on reward processing

The symptoms of emotional numbing in PTSD have been proposed to arise as a consequence of several different processes by various researchers, including chronic avoidance of trauma reminders and reactions (Keane et al., 1985), a phasic emotional absence cued by trauma contexts (Foa et al., 1992), an implicit denial process whereby the individual cuts off the experience of emotion to separate from trauma-related material (Horowitz, 1986), and context-dependent inability to access positive emotional states due to interference from incompatible cued negative affect perceptual-emotional formations (Litz, 1992). The commonality across these formulations involves the interference of negative affect (threat detection, fear, anxiety, sadness), either trauma-cued or implicit/automatic, with the elicitation and experience of positive emotion. These theories, although arising prior to the more modern advent of widespread availability of brain measurement tools, reflect neurocircuit dynamics that have been born out in empirical studies. Thus, examination of the processes underlying the interplay of negative and positive valence systems may give rise to formulations regarding how such processes may lead to the phenomenon of diminished positive affect post-trauma when taken *ad extremum*.

It is becoming abundantly clear that there are few, if any, structures of the brain that are specialized for negative or positive valence specifically. Regions heavily implicated in fear and threat processing such as the amygdala and bed nucleus of the stria terminalis are being increasingly recognized as playing an important role in appetitive behaviors and processes (Daniel and Rainnie, 2016; Kim et al., 2016a,b), while structures such as the striatum and VTA classically implicated in positive valence and reward are also being recognized to play some role in aversive behaviors (Jensen et al., 2003; Pohlack et al., 2012; Sanchez-Catalan et al., 2017). Thus, the direct interaction and reciprocal inhibition of positive and negative valence processes in the brain is increasingly plausible given the largely shared and overlapping circuitry responsible for their governance. It is therefore highly likely that an imbalance in affective valence brain systems promoted by perpetually-renewed trauma-cued stress states serves as the divergence point at which some individuals will go on to develop a post-trauma psychopathology characterized by excessive fear and anxiety responses and reduced states of pleasure and happiness.

Experimental neuroscience work has begun to elucidate the nature of these interactions between negative and positive valence systems by examining the impact of stress manipulations on subsequent reward processing behavior and circuit responses, observing that a stress manipulation prior to a reward paradigm will blunt circuitry responses to subsequent reward receipt (Porcelli et al., 2012). However, the effect of stress on reward processing may also be phase-dependent, as evidence suggests that acute psychosocial stress will enhance striatal and

amygdala responses to reward anticipation but attenuate such responses to reward receipt (Kumar et al., 2014), potentially indicating an imbalanced stress effect on incentive salience signals underlying "wanting" and consummatory "liking" of obtained rewards. Accordingly, it has been proposed that stress triggers heightened incentive salience attribution to reward-predicting cues through effects on dopamine (Mather and Lighthall, 2012), which is consistent with experimental work demonstrating acute stress increases dopamine concentrations in the rat striatum (Abercrombie et al., 1989) and alters firing rates of dopaminergic neurons (Anstrom and Woodward, 2005). Additionally, pain induction in humans has been shown to result in dopamine release using imaging of radioligand binding (Scott et al., 2006), which provides a possible neurochemical basis to explain findings for acute stress manipulations diminishing reward sensitivity, i.e. "liking" (Berghorst et al., 2013). This may occur through stress boosting incentive salience processing at the expense of complementary consummatory reward functions. In contrast, impaired reinforcement learning, which relies heavily on dopamine, has been observed in a chronically-stressed clinical population (Pechtel and Pizzagalli, 2013), which is counterintuitive to findings that dopamine is increased by acute stress and may suggest that chronic activation of stress systems promotes long-term adaptations to result in a different neural and behavioral phenotype. This latter point is supported by animal work which demonstrates that single-prolonged stress, a rodent model of PTSD, results in an anhedonic phenotype accompanied by a reduction in striatal dopamine, dopamine metabolites, and D2 receptor binding concomitant with elevated levels of dopamine transporter (Enman et al., 2015), a chemical responsible for reuptake of dopamine from the neuronal synapse. This phenotype altogether suggests a reduction in striatal dopaminergic availability following single-prolonged stress in rodents, which may be one neurochemical alteration contributing to the notable reward and positive valence abnormalities observed in PTSD (Nawijn et al., 2015). Relatedly, a neuromechanistic account has been proposed to relate chronic stress to impairment and changes in reward processing and hedonic capacity in anxiety and depression, which postulates that signals from the habenula—a very small, epithalamic structure implicated in inhibiting the VTA and its function subservient to reward processing and pleasure (Barrot et al., 2012)—excite GABA neurons in the rostromedial tegmental nucleus of the VTA, which in turn inhibit dopmaminergic VTA neurons projecting to the ventral striatum and other structures of the canonical reward circuit (Dillon et al., 2014). This model was proposed in the context of anxiety and depression, and it remains to be elucidated whether the type of stressor (extreme and punctuated as in a Criterion A traumatic event vs. more mild and chronic, as in more typical social and occupational stress) exerts divergent effects on the resulting phenotype, and how different clinical diagnoses sharing stress-related etiologies may diverge or overlap in phenotypic abnormalities.

To summarize, the relationships between positive and negative valence neural systems are just beginning to be systematically mapped and characterized. There is a great deal of work to be done in this area, which is highly germane to the study of stress-related psychopathology and the subsequent alterations in negative and positive affect. In stark contrast to depression (Pizzagalli, 2014) and early life stress (Novick et al., 2018), the study of reward and positive valence processing in the field of PTSD is not nearly as well-developed nor nuanced.

4. Reward circuit function and behavior in PTSD

Although brain imaging and electrophysiological studies of PTSD have been ongoing for decades, the affective neuroscience study of reward processing to elucidate the neurocircuitry deficits underlying diminished positive affect in PTSD is still in its relative infancy. Indeed, the first neuroimaging study specifically focused on probing positive affect in individuals with PTSD was published just over 10 years ago and was no doubt motivated by clinical observation for diminished

positive affect as a component of PTSD symptom expression and extant experimental evidence indicating mixed findings for both normal and attenuated (Amdur et al., 2000; Elman et al., 2005) behavioral and subjective emotional responses to rewarding stimulus cues. Such findings include observations that male, heterosexual Vietnam veterans (N = 12) with post-traumatic stress disorder will expend less effort (in the form of button presses) to extend the viewing time of attractive female faces relative to trauma-exposed healthy comparison veterans (N = 12), despite the fact that both groups of participants rated the faces to be similarly attractive. Additionally, more severe symptoms of PTSD were associated with the least amount of effort expenditure to continue viewing an aesthetically pleasing face of the opposite gender (Elman et al., 2005). These behavioral findings thus highlight both an abnormal and intact aspect of reward processing in individuals with PTSD, characterized by decreased effort expenditure (i.e. less behavioral manifestation of "wanting") to work for maintaining an ostensibly normative subjectively rewarding state (i.e. similar levels of "liking"). Reward processing deficits in PTSD may be particularly insidious, as some evidence suggests they persist even when the disorder has remitted (Kalebasi et al., 2015). As effort and reward computations share overlapping circuitry (Vassena et al., 2014) involving dopamine (Morita and Kato, 2018), effort expenditure *per se* could be conceptualized under the construct of incentive salience. Other behavioral studies have also produced similarly non-convergent findings for both intact and abnormal facets of reward processing, implicating reward sub-processes including diminished maintenance of effort (quick responses) over time during completion of a cognitively-demanding inhibition task with monetary incentives once the monetary incentives were removed (Casada and Roache, 2005) yet overall similar performance on reaction time measures of task engagement (Swick et al., 2012). Thus, neurocircuitry abnormalities relating PTSD to abnormalities in reward behavior and diminished positive affect symptoms are likely to be complex and context-dependent (see Fig. 2).

4.1. Early imaging studies of reward processing in PTSD

The first neuroimaging study to address this question presented 8 males with PTSD and 8 matched healthy controls a short video from a Disney movie that was reported to be a "positive-emotion-eliciting film clip" while undergoing fMRI scanning (Jatzko et al., 2006). This type of paradigm thus attempts to address the broader positive valence construct of positive emotion utilizing an ostensibly rewarding film clip. Activation during this condition was contrasted with a fixation, non-active baseline. Differences in brain activation were detected broadly throughout the brain, including decreased activation in the individuals with PTSD in the parahippocampal and fusiform gyri and bilaterally in the temporal poles. In contrast, individuals with PTSD displayed greater brain activation in regions of the lateral prefrontal, motor, and temporoccipital cortex in the right hemisphere. This study thus provided initial but cryptic evidence for brain circuitry abnormalities during passive viewing of an ostensibly enjoyable film clip. The differences in activation reported here are difficult to interpret in the absence of understanding the task main effect, and it remains unknown whether this experimental paradigm functioned as a "rewarding" stimulus or induced positive emotion *per se* in the absence of self-report or objective behavioral measures.

Later studies utilized more traditional rewards, including secondary generalized reinforcers such as money, to probe neurocircuitry in individuals with PTSD. In one such example, civilians with PTSD (N = 20) and 26 healthy controls underwent fMRI while completing a "Wheel of Fortune" type paradigm that involved passive viewing of an uncontrollable spinner and observation of rewarding or non-rewarding outcomes (Elman et al., 2009). A prior behavioral study utilizing this same paradigm observed in 15 male Vietnam veterans with PTSD relative to 11 trauma-exposed healthy veterans that PTSD was associated with a lower expectancy for monetarily rewarding outcomes prior to
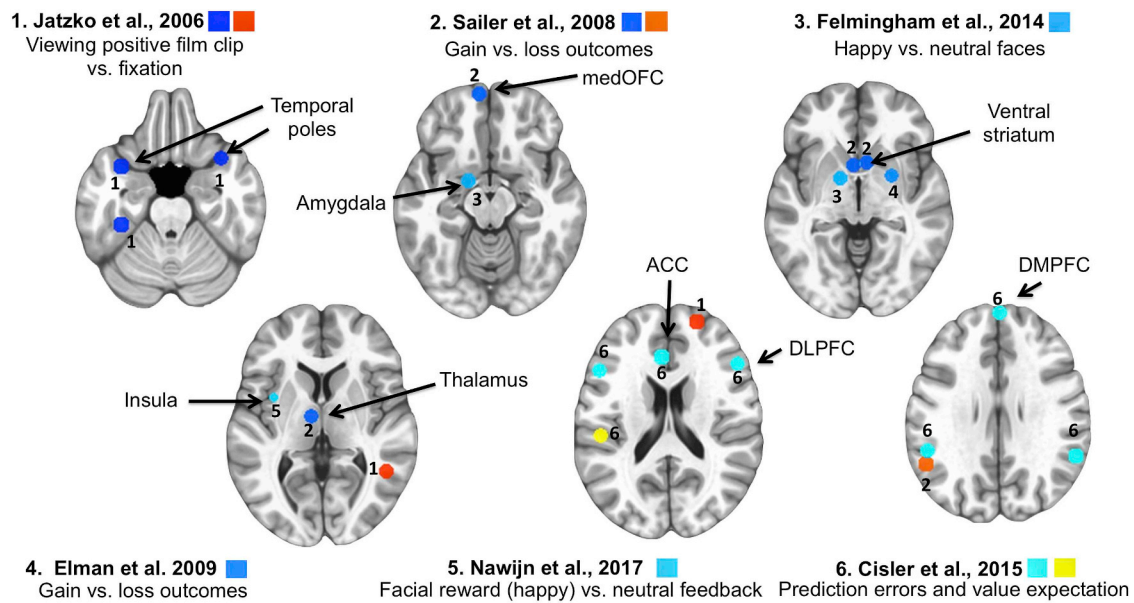
Fig. 2. Reward Processing Activation Abnormalities in PTSD
Figure depicts select loci (cluster peaks) of abnormal task activation (or reinforcement learning model parameter-modulated activation) in PTSD studies reporting voxel level results overlaid on an average anatomical image. Loci are numbered by study (see list at top and bottom) and color-coded by study and direction of abnormality. Cool colors represent loci where PTSD displayed diminished activation relative to healthy controls, and warm colors represent loci where PTSD displayed elevated activation. Note that loci of activation differences fall in regions of the canonical reward circuit (ventral striatum, medial orbitofrontal cortex, anterior cingulate) as well as subcortical (amygdala, thalamus, insula) and cortical (dorsomedial and dorsolateral prefrontal cortex) regions previously implicated in positive affect and positive emotion, more broadly. ACC = anterior cingulate cortex; DLPFC = dorsolateral prefrontal cortex; DMPFC = dorsomedial prefrontal cortex; medOFC = medial orbitofrontal cortex. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

the "spin", which could perhaps be attributed to a deficit in incentive salience or expectation of a future reward, as well as less satisfaction received from monetarily rewarding outcomes, i.e. decreased capacity for "liking", specifically when outcomes were much better than expected (Hopper et al., 2008). Thus, this paradigm would be expected to elicit abnormalities in the reward circuit in lieu of prior observations for abnormal reward processing behavior. Indeed, the individuals with PTSD undergoing fMRI while completing this paradigm displayed no differences in brain activation during anticipation of outcomes, but during the outcome phase they displayed a hypoactive ventral striatal response (caudate, putamen, and nucleus accumbens) to gains of money vs. losses of money. Moreover, larger deficits in ventral striatal activation to gains vs. losses were associated with greater PTSD symptoms of "diminished interest" and "feeling distant or cut off from others." Thus, this pair of studies provided initial evidence for a biobehavioral abnormality during a reward-processing paradigm in PTSD that was consistent in terms of behavior and circuitry. Specifically, the attenuated ventral striatal response to rewarding outcomes is consistent with the reported lack of satisfaction derived from unexpected rewarding outcomes in the behavioral study, suggesting a potential deficit in the brain's encoding of the difference between expectation for and receipt of reward, i.e. a prediction error (Garrison et al., 2013), that may be attributable to a decreased capacity to instantiate a "liking" response to the rewarding stimulus itself. Likewise, a similar deficit in striatal encoding of reward prediction errors has been demonstrated in depression (Kumar et al., 2018), though discrepant findings have also been observed (Rutledge et al., 2017). Important to note, however, is that this pair of studies used a non-instrumental reward paradigm wherein the participant's behavior had no outcome on the rewards delivered at the end of each trial. Thus, the link between these findings and computational accounts of instrumental learning, i.e. prediction errors in reinforcement learning, is only anecdotal and remains to be directly investigated.

Another study published around the same time utilized an instrumental two-choice paradigm to probe the reward circuit in patients with PTSD (N = 13) and healthy controls (N = 13) (Sailer et al., 2008). In this paradigm, individuals were presented with two numerical options on screen (one small and one large, e.g., "5" and "25") and chosen to pick one. After a delay, they were given feedback whether the amount they had picked would be added to their total or taken away from it. Thus, each trial involved an element of risk taking in terms of whether to choose the safer though less rewarding vs. the unsafe though potentially highly rewarding option. Unbeknownst to the participants, however, is that the optimal pattern for responding to obtain the most rewards and avoid the largest punishments was fixed and repeated in cycles across trials. Thus, it was possible to learn the optimal pattern of responding. The researchers observed that the acquisition of this optimal response pattern was impaired in PTSD, specifically in the second half of the task (wherein the healthy participants ostensibly learned the optimal response). This finding thus highlights a potential deficit in PTSD related to the ability to learn from past experience and utilizing learned material to predict and obtain future rewards. Brain activation to gains vs. losses was the largest in the beginning of the task in healthy controls, whereas the pattern was reversed in PTSD. Specifically, in the first half of the task individuals with PTSD displayed greater activation in dorsal prefrontal and parietal portions of the brain in response to gains (potentially reflecting a greater contribution of cognitive processing) whereas in the second half of the paradigm they displayed a relative lack of activation in canonical reward circuit regions including the ventral striatum and medial orbitofrontal cortex, consistent with an impaired reward circuit response to the "liking" phase of reward consumption. The findings of this study thus replicate the findings of the aforementioned studies, i.e. a hypoactive ventral striatal response to reward receipt. However, this convergence is tempered by the fact that learning deficits were apparent in individuals with PTSD and they thus obtained fewer rewards than the healthy controls, a learning deficit which in itself could account for the brain activation abnormalities to reward receipt. Put differently, the quantity of reward circuit

engagement may be reflected in these findings rather than the quality, which confounds interpretation of the two processes. Nevertheless, convergent data indicates somewhat consistent biobehavioral abnormalities for a hypoactive reward circuit and diminished subjective "liking" response to classic rewards in individuals suffering from PTSD.

4.2. Reward circuit abnormalities and diminished positive affect trauma symptoms

Reward circuit biological abnormalities in PTSD are likely to underlie specific facets of trauma symptomatology, most prominently the symptoms typically classified as "emotional numbing" in the DSM-IV diagnostic system (APA, 2000), now considered to be "negative alterations in cognition and mood" in DSM-5 (APA, 2013). These symptoms encompass specific facets of diminished positive affect, such as difficulty experiencing happiness, joy, and other positive emotions; diminished interest in pleasurable activities; and inability to have loving or close feelings in relation to friends and significant others (a distinctly social form of reinforcement). Several investigations have attempted to link these symptom facets to reward-related biological processes in the hopes of better elucidating the pathophysiological mechanism underlying their manifestation. In an electrophysiological investigation, experimenters assessed 51 individuals with varying levels of post-traumatic stress symptoms as part of an ongoing study of anxiety and depression (Lieberman et al., 2017). They administered two tasks designed to probe reward and threat processes, of which the reward paradigm was a two-choice paradigm with a fixed reinforcement schedule (half of trials were rewarded and half were punished, regardless of choice). The outcome measure of interest was the reward-related positivity, an event-related potential (ERP) measured using electroencephalogram (EEG) during receipt of rewards in the context of this paradigm. The authors observed that a measure of PTSD symptom severity for the DSM-5 domain encompassing diminished positive affect symptoms was specifically associated with a diminished magnitude of the reward-related positivity ERP, even after controlling for other symptom dimensions and demographic covariates. This study thus presents suggestive evidence that a biomarker of diminished positive affect symptoms, specifically an impaired brain response during the "liking" phase of reward consumption, may be possible to identify and develop into a useful clinical tool. However, this contention is also tempered by the fact that this sample was composed primarily of individuals with mixed anxiety and depression, only about 1/3 met criteria for PTSD, and only 10% of the entire sample presenting with PTSD as the clinically-predominant disorder. This study also did not assess the subjective affective response to reward receipt, which would provide a more direct measure of the degree of intact hedonic capacity. Future studies in more PTSD-predominant clinical samples are needed to replicate and extend these findings.

Other investigators have utilized fMRI as a convergent measure to identify circuitry signatures of diminished positive affect symptoms in PTSD. Utilizing the older DSM-IV conceptualization of emotional numbing, one study investigated how processing of positive facial affect, i.e. happy/smiling faces, might distinguish neurocircuitry responses between PTSD and trauma-exposed healthy controls and how these responses might relate to emotional numbing symptoms (Felmingham et al., 2014). The experimenters recruited civilians with PTSD (N = 23) and trauma-exposed healthy controls (N = 20) and administered a fMRI paradigm consisting of passive viewing of happy and neutral faces. Contrasting responses to the two, the experimenters observed that individuals with PTSD rated the happy faces as less "intense", consistent with a consummatory "liking" reward-processing deficit, and also displayed attenuated activation in the ventral striatum to happy vs. neutral faces. Moreover, the greater the deficit in left ventral striatal response, the more severe the symptoms of emotional numbing in the PTSD participants. The effect of comorbid major depression in this sample was also investigated, demonstrating that PTSD

participants both with and without comorbid major depression both displayed abnormal ventral striatal responses to happy vs. neutral faces (albeit effects were more prominent for those with depression). These findings should be considered preliminary, however, as stringent correction for Type I error was loosened here. Moreover, although happy faces are generally considered to be a form of socially-rewarding stimuli and engender positive emotion in the recipient (Wild et al., 2001), it remains inconclusive whether these stimuli were processed as such in this study.

Another fMRI study examined the relationship between emotional numbing symptoms and brain activation in individuals with PTSD, this time utilizing affective script driven imagery of both positive and negative valence with social and non-social content in women with (N = 14) and without (N = 16) childhood maltreatment-related PTSD (Frewen et al., 2012). Individuals listened to a series of scripted stories, imagined they were occurring, experienced their emotions in response to the stories, and then afterwards rated the level of emotion experienced. The experimenters then correlated severity of emotional numbing symptoms with brain activation in select regions of interest while controlling for comorbid depression symptoms. The authors observed that self-reported positive emotional responses to positive scripts (both social and non-social) were negatively correlated with severity of emotional numbing symptoms. This finding thus establishes the expected negative relationship between numbing symptoms and capacity for positive emotions. Likewise, the authors observed a specific negative relationship between emotional numbing symptoms and brain activation in the dorsomedial prefrontal cortex in women with PTSD during positive social (but not non-social) scripts. This anterior and superior region of the medial prefrontal cortex is not typically implicated in reward processing per se, but it has been implicated in social cognition and social processes more broadly (Ghosh et al., 2012; Knutson et al., 2008) as well as positive emotion induction more generally (Speer et al., 2014), thus highlighting a potential substrate responsible for the integration of social cognition and positive emotion. Given that disrupted social relationships fall within the same broad category of positive valence deficits in PTSD diagnostic systems (APA, 2000, 2013), the involvement of more extended social cognitive circuitry in mediating positive valence deficits relating to social interaction is plausible and interesting. However, the findings from this study are tempered by the small sample size and the fact that neurocircuitry responses to affective scripts may not be a generalizable measure of real-world affective and social functioning.

4.3. Novel pharmacological modulations of the reward circuit in PTSD

Novel pharmacological manipulations of the reward circuit have recently been proposed to enhance psychotherapy for PTSD. One such substance is the neuropeptide oxytocin (Olff et al., 2010), an endogenously-produced chemical which plays an important role in social bonding behavior (Baumgartner et al., 2008) and binds to specific receptors in the brain that modulate or augment fear and reward processing circuitry (Kirsch et al., 2005). The rationale put forth is that oxytocin changes the balance of approach/avoidance behavior by enhancing function of approach-related neurocircuitry and attenuating that of fear and avoidance-related circuitry, which is consistent with extant experimental findings for oxytocin boosting reward circuit activation in response to rewarding stimuli and attenuating responses in fear and threat-related circuitry to experimental threat cues (Harari-Dahan and Bernstein, 2014). Thus, oxytocin administration prior to PTSD psychotherapy might enhance the ability of the individual to benefit from the mechanism of exposure-focused interventions (Olff et al., 2010), which are thought to occur via increasing one's ability to feel safe when presented with stimuli previously associated with fear responses (Foa and Kozak, 1986). A pair of imaging studies has investigated the enhanced reward circuit mechanism of this hypothesis by administering intransal oxytocin to participants with PTSD during

reward processing paradigms. In the first study examining brain responses to anticipation and receipt of monetary reward in 35 police officers with PTSD and 37 trauma-exposed healthy comparison officers, the experimenters observed a main effect of oxytocin vs. placebo administration on brain responses during anticipation of rewards and losses irrespective of group, but not a group × drug interaction effect (Nawijn et al., 2016). However, oxytocin administration obliterated the negative relationship observed under placebo between left striatal responses during reward anticipation in PTSD with severity of the PTSD symptom of diminished interest in pleasurable activities, suggesting that oxytocin may exert some benefit on processing of incentive salience signals, i.e. cues that engender pursuit of a reward, via striatal mechanisms for those individuals displaying the greatest impairment in incentive salience processing. In a second study examining brain responses to social reward (happy/smiling faces) in PTSD in the same sample of police officers, the experimenters observed a reward-related deficit in left anterior insula activation to receipt of social rewards under placebo (Nawijn et al., 2017), suggesting an impairment in the circuitry underlying the "liking" phase of reward consumption. When oxytocin was administered, however, there was a significant group × drug interaction such that individuals with PTSD displayed less deactivation during reward receipt in the left putamen, as well as a trend for increased activation in the left anterior insula, which overlapped with the deficit observed between PTSD and TEHCs. However, there was no effect of oxytocin on subjective ratings of the faces themselves in or across groups (i.e. "liking" of the rewarding stimulus), nor a group × drug interaction, which raises the question of whether the brain activation changes observed here reflect reward-related "liking" activity *per se* or are more specifically related to social cognitive or face feature processing. This could have been examined by contrasting the rewarding (happy faces) and punishing outcomes (angry faces) directly for differential effects while controlling for face processing more generally. Additionally, the lack of an oxytocin effect on neural or behavioral responses to monetary reward also suggests oxytocin was exerting a more selective effect on social cognitive processes in the second study as opposed to reward and subjective "liking" responses *per se*. Nonetheless, these findings represent the strongest evidence to date for the demonstrated potential in utilizing novel pharmacological intervention approaches to augment positive valence processing in PTSD and the neurocircuitry dynamics that might underlie such changes.

Although the imaging literature on pharmacological PTSD treatment or treatment augmentations is relatively small in scope (MacNamara et al., 2016; Nawijn et al., 2016, 2017), there are numerous other notable drugs that show potential PTSD therapeutic efficacy worthy of mention here, particularly since evidence suggests they operate via mechanisms which include the reward circuit and positive valence. Chief among these is ± 3,4-methylenedioxymethamphetamine (MDMA), commonly know as "ectasy" or "Molly" when utilized as a recreational drug of abuse. MDMA is currently being investigated as an adjunct to psychotherapy and has demonstrated initial efficacy for treatment-resistant PTSD (Amoroso and Workman, 2016; Mithoefer et al., 2018; Mithoefer et al., 2011; Oehen et al., 2013). This treatment modality has been designated as a "breakthrough therapy" by the Food and Drug Administration (FDA) and has been fast-tracked for approval as an FDA-approved treatment for treatment-resistant PTSD. It is currently being tested in Phase 3 clinical trials (Bedi, 2018). Unlike existing paradigms for chronic dosing of medications in treating psychiatric disorders, MDMA-assisted psychotherapy adopts the classic psychedelic-assisted psychotherapy model (Pahnke et al., 1970), wherein therapeutic change is effected through 2 to 3 long, high-dose drug psychotherapy sessions with preparatory therapeutic sessions beforehand and integration sessions afterwards. The mechanism of the MDMA therapeutic effect in PTSD is currently unknown, but experimental evidence suggests MDMA exerts prominent prosocial effects in animals and humans, involving enhanced responses to social rewards,

decreased aggression, and enhancements in prosocial feelings and behaviors (Kamilar-Britt and Bedi, 2015). These behavioral effects are plausible given MDMA has been shown to impact a diverse array of neurotransmitter systems known to be involved in reward, social behavior, emotion, and mood, including serotonin transporter function, dopamine type 2 receptors, serotonin type 2 receptors, and oxytocin release (Amoroso and Workman, 2016). Neuroimaging work in healthy volunteers demonstrates that MDMA enhances ventral striatal responses to happy facial affect and attenuates amygdalar responses to angry facial affect (Bedi et al., 2009), which suggests one potential affective neuromechanistic pathway underlying therapeutic effects in PTSD, given that PTSD is associated w/reduced ventral striatal responses to happy faces (Felmingham et al., 2014) and elevated amygdalar responses to angry faces (Fonzo et al., 2010). MDMA, in healthy individuals undergoing imaging, has also been demonstrated to augment resting cerebral blood flow and connectivity within the ventromedial prefrontal cortex and a midbrain region that may encompass the ventral tegmental area (Carhart-Harris et al., 2015), both nodes of the canonical reward circuit. Pre/post-therapeutic imaging studies in individuals with PTSD undergoing this treatment are ultimately needed to better discern potential mechanisms of action and whether these occur through impacting reward circuitry function and positive affect/emotion, more generally.

MDMA, though a derivative of methamphetamine, is thought to work through a more diverse set of neurotransmitter pathways than that of classical amphetamine-type drugs, which have as their proposed mechanism of action the inhibition of dopamine and norepinephrine reuptake as well as inhibition of monoamine oxidase, an enzyme responsible for the breakdown of monoamine neurotransmitters. Methylphenidate, a common prescription stimulant drug for the treatment of attention deficit hyperactivity disorder (ADHD), likewise shares a mechanism of action involving reuptake inhibition of dopamine and norepinephrine (Faraone, 2018). Interestingly, both methylphenidate and amphetamine have demonstrated some indication of promise for treating PTSD, with methylphenidate showing positive benefits with a large effect size on PTSD symptoms in a small, randomized clinical trial (McAllister et al., 2016). Likewise, a preclinical study utilizing the single-prolonged stress rat model of PTSD demonstrated that a single amphetamine injection offered in the trauma context to those rats shown to be susceptible to developing the PTSD phenotype abolished all symptoms and rendered them indistinguishable from the resilient rats (Toledano and Gisquet-Verrier, 2014). These findings are intriguing and warrant further investigation of non-empathogenic psychostimulants as therapeutic tools in treating PTSD, an observation that was noted in a case report almost twenty years ago (Daly, 2000). As both MDMA and non-empathogenic psychostimulants share modulation of dopamine function as a key mechanism of psychoactive effect, a manipulation known to impact positive valence and reward systems (Berridge, 2007), these pharmacological findings further implicate reward circuitry and positive valence processing as a key therapeutic target for PTSD in need of further development. In particular, as hypothesized by Toledano and Gisquet-Verrier (2014), the delivery of amphetamine in the trauma context may have abolished symptoms by pharmacologically promoting positive affect in a context learned to be incompatible with this emotional response, thereby necessitating memory remodeling via reconsolidation processes. This hypothesis highlights a potential convergent mechanism of action for both MDMA-assisted psychotherapy and non-empathogenic psychostimulant medications.

Finally, drugs that activate or modulate endocannabinoid receptors, most famously Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD), demonstrate promise as a class of therapeutic substances for PTSD (Loflin et al., 2017). Controlled studies investigating smoked or inhaled cannabis are currently in development, and observational evidence suggests cannabis can promote substantial degrees of PTSD symptom reduction (Greer et al., 2014) and is being increasingly employed for

symptom coping-reasons amongst individuals with PTSD symptoms (Bonn-Miller et al., 2014). The synthetic cannabinoid agonist, nabilone, has also demonstrated evidence for efficacy in treating PTSD-related nightmares (Jetly et al., 2015). There is abundant experimental evidence to indicate that cannabinoids modulate PTSD-relevant neurocircuitry function, including attenuating amygdalar responses to social signals of threat (Phan et al., 2008) and increasing ventromedial prefrontal cortex and hippocampal activation during fear extinction recall (Rabinak et al., 2014), both of which are theorized to be core deficits underlying exaggerated fear responses in PTSD (Milad et al., 2014). Relevant to positive emotion, however, are findings that THC administration alters brain activation in healthy controls during a reward anticipation paradigm (van Hell et al., 2012), but only during the outcome phase of the trial and not during anticipation (suggesting a modulation of consummatory processing rather than valuation or incentive salience) and only in regions outside the canonical reward circuit. However, another study demonstrated that THC attenuated ventral striatal activation during retrieval of previously-learned word pairs in healthy controls, demonstrating a modulation of reward circuitry but outside of a reward processing behavioral context (Bhattacharyya et al., 2009). Thus, evidence for modulation of reward circuitry in a reward processing context by endocannabinoid-modulating drugs remains equivocal, though supportive evidence for endocannabinoid brain function in mediating reward circuit responses is more robust, demonstrating that genetic variation in endocannabinoid-related genes is associated with differential brain activation to socially rewarding cues, such as happy faces, in both healthy individuals and those with depression (Chakrabarti et al., 2006; Domschke et al., 2008; Hariri et al., 2009). Moreover, cannabinoid receptor binding potential in PTSD is elevated alongside decreased levels of peripheral circulating endocannabinoids (Neumeister et al., 2013), which further highlights the potential therapeutic relevance of this system to post-trauma psychopathology. It should also be noted that therapeutic cannabinoid modulation is complex, with opposite effects sometimes observed for the two most common natural endocannabinoid modulators (THC and CBD)(Bhattacharyya et al., 2015; Bhattacharyya et al., 2010; Fusar-Poli et al., 2009). Thus, efforts to optimize the field of therapeutic endocannabinoid modulation to remediate the desired symptom or circuit deficit is likely to be ongoing for some time. However, given existing evidence for endocannabinoid system alterations in PTSD (Neumeister et al., 2015) as well as the central role of endocannabinoids in mediating the subjective experience of pleasure (Berridge and Kringelbach, 2015; Mahler et al., 2007), this system remains extremely promising as a future pharmacological target.

4.4. Integrating computational models of reinforcement learning with imaging: dysfunctional representation of reward-related information components in PTSD

Recent advances in clinical neuroscience have highlighted the value of algorithmic decision-making computational models for elucidating information processing dysfunction in psychiatric disorders (Huys et al., 2016; Montague et al., 2012; Wang and Krystal, 2014), allowing for the separation of abnormalities within disorders by both temporal phases of decision-making (e.g., anticipation, decision, receipt) as well as by type of information processed (e.g., evaluating outcomes and learning from them vs. employing prior knowledge to choose actions). Such an approach greatly improves the inferential power afforded by observational studies, allowing researchers to better isolate mechanistic processes contributing to psychopathology through teasing apart contributions of these various processes to the observed phenotypes.

In the field of reward processing, these algorithmic decision-making models have been heavily applied to reinforcement learning (see Section 2.3), specifically by employing mathematical formulae to symbolize the information processing computations underlying decision-making, modeling individual behavior with Bayesian statistical

techniques to derive weights for the different terms or information components contained within the mathematical model, and then regressing imaging data against these component weights on a trial-by-trial basis to identify brain signals corresponding to these information processing parameters and how the degree of the modulation of the brain signal by these parameters may differ across patient groups. This latter approach is known as "model-based imaging" (O'Doherty et al., 2007), and it provides an integrative account of how unobservable information processing, inferred from observed behavior, may be abnormally instantiated in definable neurocircuitry.

Recent work has exploited this approach in studying reward-related decision-making in PTSD, both in response to social and monetary rewards. Utilizing a two-arm bandit task (i.e. participant has a choice between two options on each decision portion of the trial and is attempting to pick the option that provides the largest monetary payoff in the outcome phase) in women with PTSD due to assault, the investigators examined how computational estimates of stimulus value (the degree to which a particular choice stimulus during the decision phase was perceived to be associated with likelihood of a future reward) and prediction errors (the difference between the outcome expected and the outcome received) differed as a function of diagnostic status, as well as how the information components of value and prediction errors may be differentially reflected in brain circuitry (Ross et al., 2018). The authors utilized the common Rescorla-Wagner computational model of reinforcement learning (Sutton and Barto, 1998) to derive trial-by-trial estimates of stimulus value and prediction errors for each individual, and then examined how these component estimates related to time courses of BOLD activity (separated by independent component analysis-defined spatial networks) throughout the course of the task. The authors observed no differences in value or prediction error parameter estimates between women with PTSD and healthy controls, but they did observe a selective deficit in the degree to which the ventral striatum/medial prefrontal cortex network and the anterior insula network showed modulation of BOLD signal by positive prediction error encoding, i.e. the degree of BOLD signal change as a function per unit increase in positive prediction error (when decision outcome was better than expected) was reduced relative to healthy controls. These findings, though exciting and novel, are tempered by the small sample size, the lack of a trauma-exposed comparison group (thus rendering the effects non-specific to psychopathology *per se*), and the lack of significant findings utilizing a voxel-level whole brain analysis. However, they do provide initial evidence for a specific information processing dysfunction during the outcome phase of reward processing in circuitry previously implicated to display outcome-related reward abnormalities, i.e. the ventral striatum.

The authors also examined this same sample in a related paradigm that attempted to address the social deficit symptomatology observed to be characteristic of PTSD (Cisler et al., 2015). Specifically, the authors utilized a behavioral Trust Game completed outside the scanner in which participants invested a chosen amount of money into another "player" on each trial (which was, unbeknownst to them, actually a computer), and could receive back a portion of the tripled investment dictated by the other player on each trial. The trials began by the participant receiving back somewhere between 40 and 60% of the investment, which then precipitously dropped on the next set of trials to 10–30%, and later returned back to baseline on the last set of trials. The goal here was to establish how social norm i.e. "trust" violations, would impact subsequent investments. After this, participants completed a social reward learning paradigm inside the scanner, which was a two-arm bandit ask (as in the prior study). However, this time two faces were utilized as predictive cues, and rewards were "smiles" from these faces instead of money (as in the prior task). The authors utilized a similar reinforcement learning (Rescorla-Wagner) model on the Trust Game behavioral task as well as the social reward two-arm bandit task. In the Trust Game, the PTSD group displayed significantly lower estimates of learning rate (the degree to which a surprising outcome is

utilized to update the value for the stimulus predicting that outcome in future trials) and an attenuated effect of prediction errors on the value estimate for the chosen decision on the subsequent trial, altogether suggesting a diminished ability to incorporate past experience into updating expectations. In the social reward paradigm, PTSD displayed elevated encoding of prediction errors in the temporoparietal junction, while the encoding of stimulus value was diminished in PTSD in the medial prefrontal cortex as well as the dorsolateral prefrontal cortex and temporoparietal junction. Additionally, when comparing computational parameter estimates between the Trust Game and the social reward paradigm, the authors observed that the greater the effect of the prediction error (i.e. Trust violation) on the value expectation for the chosen investment on the next trial, the greater the deficiency of expected value encoding during the decision phase on the social reward learning paradigm. This latter finding was suggested by the authors to indicate that ostensibly social learning processes can influence subsequent deficits in social reward and social-specific PTSD symptomatology, although the degree to which the Trust Game can be considered a probe of social processes and the degree to which the social learning paradigm was motivated entirely by social rewards (participants were incentivized with a monetary reward corresponding to the number of smiles earned) is questionable. Likewise, the generalizability of these findings to PTSD in general may be limited, given that the patient sample was composed entirely of women with PTSD related to interpersonal assault, a specific trauma type that may exert more focused detrimental effects on the subsequent processing of social information. Nevertheless, these findings implicate reward circuit dynamics as a concomitant of reward processing abnormalities in PTSD, convergent with prior work, and furthermore extend the literature by providing evidence for dysfunctional instantiation of reward-related information processing components in relative circuitry.

4.5. Interim summary

The modest literature that has accumulated investigating reward processing behavior and circuit dynamics in PTSD has demonstrated mixed evidence for abnormalities in individuals with PTSD relative to both trauma and non trauma-exposed healthy controls during various temporal phases of reward processing (e.g., anticipation and receipt) as well as during processes potentially reflecting the subjectively discernible "wanting" and "liking" components of positive valence. This evidence is mixed both in regard to both presence and absence of abnormalities, as well as the specific behavioral and circuit dynamics implicated as abnormal across studies. The most consistent finding across studies and paradigms is a hyporesponsivity of the ventral striatum to monetary and "social" reward receipt (Elman et al., 2009; Felmingham et al., 2014; Ross et al., 2018; Sailer et al., 2008), which is consistent with the motivational deficits, diminished interest (as diminished subjective "liking" of a reward will induce less motivation or interest in obtaining that reward in the future), and diminished capacity to feel positive emotions that are frequently observed to characterize individuals with the PTSD diagnosis (Hassija et al., 2012). Moreover, greater severity of PTSD diminished positive affect symptoms were observed to relate to more severe deficits in ventral striatal engagement to both monetary and social reward (Elman et al., 2009; Felmingham et al., 2014), which further highlights the plausibility of this convergence. However, these conclusions must be taken lightly given the significant limitations of the extant literature, including small sample sizes (Elman et al., 2009; Sailer et al., 2008), lack of rigorous false positive control (Felmingham et al., 2014), and lack of demonstrated generalizability of task metrics to ecologically-valid measures of positive affect and social adjustment (e.g., quality of social relationships, ecological momentary assessments of positive affect in daily life, measures of functional capacity, etc.). Although these initial findings are promising in highlighting circuit deficits in PTSD that relate to diminished positive affect symptoms, much more work is needed to develop

this field of study into one capable of producing clinically-relevant and clinically-actionable deliverables that will transform and improve trauma mental health care. In the following section, specific guidelines are offered for this purpose.

5. Future directions in trauma affective neuroscience research: towards a clinically relevant, bivalent, integrative model of post-trauma symptomatology

As stated earlier in this manuscript, the primary purpose of this commentary and review was to assess the field's progress in understanding the biological and behavioral mechanisms underlying post-trauma diminished positive affect, synthesize what is known into a brief but informative summary, and advocate for the prioritization of this line of study into one of greater importance in the field at large. In support of the latter goal, below is a list of recommendations and brief justifications for best research practices that will expedite this process, thereby leading to an accelerated discovery of knowledge and rapid advancement of scientific understanding.

5.1. Use ecologically valid reward stimuli in multiple sensory modalities to facilitate generalizability of laboratory findings

It is noteworthy that the majority of PTSD imaging studies assessing reward processing and diminished positive affect symptoms have utilized stimuli that provoke, at most, a mild elevation of positive affect, including positive pictorial stimuli such as smiling/happy or attractive faces (Elman et al., 2005; Felmingham et al., 2014; Nawijn et al., 2017) and modest monetary rewards (Elman et al., 2009; Hopper et al., 2008; Nawijn et al., 2016). However, the range of rewarding stimuli available to an individual in day-to-day life, as well as those that are "pursued" or "consumed," is of a much broader and multimodal scope. In particular, diverse rewarding stimuli such as pleasant tastes (McClure et al., 2003), odors (Sorokowska et al., 2016), touch (Davidovic et al., 2017), music (Zatorre and Salimpoor, 2013), humorous stimuli (Mobbs et al., 2003), erotic stimuli (Brand et al., 2016), and genital vibratory stimulation (Prause et al., 2016) have all been successfully employed with neuroimaging and have demonstrated engagement of mesolimbic and extended reward circuitry components. Thus, expanding the modalities and types of stimuli utilized to engage reward processes in individuals with PTSD is likely to provide a richer and more meaningful picture of the spectrum of brain dynamics implicated in diminished positive affect symptoms, which range from more primary impairments such as anhedonia (Olson et al., 2017) to deficits in specific types of reward modalities, e.g. intimate relationships and romantic love (DiMauro et al., 2018). Such a broad battery of engagement is likely to provide the most complete assessment of the various neurocircuitry facts that underlie impairments in reward processing that are both common across rewarding stimuli as well as specific to a sensory modality or stimulus quality.

5.2. Use tasks and paradigms with the capacity to dissociate different phases or behavioral processes involved in anticipating, consuming, and learning to obtain rewards, as well as positive affect more generally

Reward processing is an experimental construct with numerous components, distinct temporal phases, and concurrent processes supporting its function within the organism. These include numerous distinct conglomerates of organism-environment interactions such as processing cues that predict potential future rewards, making decisions amongst various behavioral options to pursue or obtain rewards, implementing a behavior or sequence of behaviors to obtain a reward, anticipating a reward once a behavioral repertoire is engaged, assessing the outcome of a behavior and the rewards received, reward consumption and hedonic value, and consolidating information and learning from experience how to obtain rewards in the future. Given the

modest extant literature on reward processing in PTSD, it remains uncertain which of these temporal phases and component processes are normal or abnormal and how each relates to specific components of diminished positive affect symptoms. Thoughtful design of behavioral paradigms and experimental manipulations to dissect these components and assess the intactness of each in future studies will allow for precision mapping amongst behavioral and psychological processes, neural circuitry, and disturbances in positive affect and adaptive function that characterize the PTSD phenotype. Likewise, the gaps between reward processing, positive emotion, and positive affect more generally remain to be bridged. Thus, utilizing paradigms that conceptualize and probe diminished positive affect from more than a purely reward processing deficit perspective will be particularly important to understanding how these levels relate to one another and how circuit deficits manifest across them.

5.3. Further exploit theory-driven computational methods to bridge neural and behavioral units of measurement and facilitate inference on information processing abnormalities and their relevance to clinical symptoms, functional impairment, and reward circuit dynamics

Initial efforts in PTSD to utilize theory-driven computational models to infer latent parameters of information processing involved in reward-based decision making have already surfaced (Myers et al., 2013), including the integration of these models with imaging data to bridge behavioral and brain-based units of analysis (Cisler et al., 2015; Ross et al., 2018). Such an approach holds tremendous value for advancing the field of biological psychiatry more generally (Montague et al., 2012; Wang and Krystal, 2014) but also for PTSD and trauma affective neuroscience research more specifically for several reasons. First, the study of psychiatric phenomena is extremely complex, necessitating an understanding not only of the brain, how it functions, and how it gives rise to behavior, but also how these functions interact with and are sustained by complex environmental feedback loops through bidirectional information flow between organism and environment (Borsboom et al., 2018; Huys et al., 2016). This is particularly the case in post-trauma psychopathology, where the structure and emergence of symptoms is largely dictated by trauma-related environmental cues eliciting intrusions and other re-experiencing phenomena in the acute and chronic phases of the disorder, while social detachment and emotional numbing constitute another prominent, but somewhat distinct, symptom set reflecting a lack of adaptive engagement with the environment (Bryant et al., 2017). Thus, understanding the relationships among complex environments, brain function, and the resultant symptom expression is of paramount importance to efforts at identifying biological or behavioral targets for remediation. Computational approaches facilitate this effort by allowing for data-driven (see Section 5.5) and theory-driven approaches at connecting across various measurement units (context-bound behavior, brain dynamics, symptoms, etc.) in order to facilitate measurements of variables that are otherwise unobservable or unmeasurable (Huys et al., 2016). In the case of theory-driven models, model testing and fitting is usually guided by imposed constraints that attempt to optimize some quanta of importance (Montague et al., 2012). When utilizing Bayesian models to understand the structure of information computations underlying behavior, the observed behavioral data is assessed in relation to some optimal solution predicted by the model (Huys et al., 2016). Model fitting and testing proceeds by assessing adequacy of model fit to the data, penalizing for complexity, and ultimately arriving at the most parsimonious description of the information processing imposed by the model structure that best explains the observed data. Such an approach is advantageous by virtue of its parsimony while still maintaining a meaningful theoretical structure that allows for dissociable inferences on separable components.

Second, through this imposition of meaningful theoretical structure on what appears to be chaotic behavior, such a modeling approach allows for the disaggregation of different temporal and theoretical components that contribute to an observed outcome. In the case of reward-based decision-making, these components correspond to temporally-distinct, theoretically and biologically-meaningful dissociable processes involving valuation of some predictive cue, enacting a decision policy, and learning from outcomes to inform future behavior (Montague et al., 2012). Recent work in this field has demonstrated that such approaches can be used to parse effects of different normative psychological functions (Daw, O'Doherty et al., 2006; Harlé et al., 2013; Roy et al., 2014), psychopathology dimensions (Harlé et al., 2017), or diagnostic-based abnormalities (Huys et al., 2013; Ross et al., 2018) on particular components of the decision-making process, thus allowing for a much more meaningful approach to dissecting behavior to inform clinical theory. Similar work has also highlighted a basic distinction in the way that the human brain utilizes learning and past experience to make decisions. These two canonical modes, known as model free or model based learning, are distinguished by the degree to which an internal schematic model or representation of the environment is utilized to inform the decision. This distinction has been not only extremely informative in terms of understanding basic human neuroscience and behavior (Daw, O'Doherty et al., 2006; Kovach et al., 2012), but also how such basic distinctions in decision making relate to an endophenotype of psychopathology that cuts across diagnostic categories: compulsivity (Voon et al., 2014), which appears to be characterized by a tendency towards elevated reliance on model-free learning alongside structural abnormalities in cortico-striatal circuitry. This example illustrates how computational approaches can dissect components of information processing underlying human cognitive function and how dysfunction in such components can underlie common transdiagnostic elements of psychopathology.

Third, such theory-driven computational approaches not only produce information at one level of analysis that can bridge across other levels, but also provide descriptive and inferential power through application at multiple levels concurrently (Wang and Krystal, 2014). In addition to theory-driven models of psychological phenomena such as decision-making, such models can also be applied to describe the behavior of biological structures themselves (e.g., circuits, neurons, etc.), which yields biophysical models capable of informing predictions regarding potential therapeutic perturbations, such as activation of receptor targets by drug ligands, as well as models capable of informing understanding of both circuit function and behavioral phenomena (Wang and Krystal, 2014). A notable example of this multi-level application is the development of a microcircuit model of working memory during the oculomotor delayed-response experiment (Compte et al., 2000), which links an observable behavior (eye saccades) to a psychological construct (working memory) through a specific set of receptor-mediated neuronal processes (recurrent excitation via NMDA receptors) via a multicolumn biophysical model of the cortex. Furthermore, this same model has been applied to explain behavioral dysfunction in schizophrenia by incorporating disinhibition of NMDA receptors in the model, which produces the expected behavioral output in simulation that was verified experimentally through use of ketamine in healthy volunteers (an NMDA-receptor antagonist)(Murray et al., 2014).

In summary, the area of computational psychiatry remains ripe with scientific possibility for well-designed experiments to potentially provide very useful and clinically relevant information to advance the field. In particular, the field of post-trauma psychopathology stands to benefit from these methodological innovations through using modeling to emphasize and promote meaningful theoretical dissection of the feedback loop components between organismic (biological and behavioral) processes and complex environments (to which the posttraumatic stress phenotype is intimately tied). In the case of understanding diminished positive affect, it will be paramount to understand how specific aspects of symptomatology relate to and are perhaps mediated by specific component processes elucidated by these models, which will yield testable targets for behavioral or biological intervention efforts.

Importantly, these efforts should focus on traversing multiple units of analysis, ideally incorporating and bridging across models of the following levels: a) microcircuit-level models informed by receptor binding potentials (e.g., D1 and D2 receptors in the mesolimbic dopamine system); b) macrocircuit models of excitatory and inhibitory connections amongst circuit nodes, elucidated via neuroanatomical work in animals, models of statistical causality in imaging such as dynamic causal modeling (Friston et al., 2003), and perturbation based methods for probing causal connectivity such as transcranial magnetic stimulation (Chen et al., 2013); and c) models of reward-related decision-making behavior that inform on environmentally-contingent and context-dependent theoretical information components (such as expected value and prediction errors). The combination of these models across units of analysis would facilitate a deep understanding of how observed behavior arises out of reward-related information components instantiated within a particular brain region or circuit over time and how the propagation of information amongst circuit nodes influences and is influenced by biology (circuit integrity and neurochemistry), environment, and behavior. When examined in relation to facets of symptomatology, this approach could yield several tractable targets for intervention development.

5.4. Move beyond sole self- or clinician-rated symptom outcomes and relate laboratory measures to more proximal, "real-life" metrics of positive affect, quality of life, social relationships, and functional capacity

This recommendation carries a larger scope than that of diminished positive affect in PTSD, specifically, but it is highlighted here due to the wide variability in the individual's life factors that contribute to the individual's life satisfaction and overall well being. Thus, beyond clinical measures of anhedonia, emotional numbing, and depressed mood, there exists a multitude of other measures, outcomes, and processes that are directly germane to understanding how positive affect manifests outside the laboratory and influences one's ability to enjoy life, form and maintain social relationships, derive meaning, and successfully navigate financial and occupational challenges. For example, none of the studies in the extant literature investigating PTSD, reward, and positive affect have attempted to link laboratory measures to more ecological assessments of positive emotion in daily life. Given the recent explosion in biometric or mobile assessment and passive data collection through devices such as wearable technologies, smart phones, internet reporting tools, etc., the possibility of measuring clinically-relevant variables rapidly and repeatedly and having them inform and complement experimental findings is now an emerging reality (Bourla et al., 2018). Thus, it is anticipated that the integration of laboratory neuroscience techniques with the "big data" afforded by easily collected, repeated, and rapidly acquired biometric and ecological momentary assessments will help to ground the evolving neurocircuitry findings within a multimodal measurement framework that better represents the factors contributing to or influencing real-life outcomes.

5.5. Make use of individual differences, multidimensional data, and massive multivariate analytics to understand how individual characteristics of circuit function, symptoms, and behaviors influence one another, and develop biomarkers for specific dysfunctional psychological processes that relate to specific diminished positive affect symptoms

Given the extreme degree of clinical heterogeneity that characterizes the PTSD diagnosis (Galatzer-Levy and Bryant, 2013), any conceptual model of how trauma neurocircuitry mechanisms govern symptom expression that does not account for individual variation is unlikely to be useful in making accurate predictions or guiding treatment development. Thus, it could be argued that it is no longer sufficient to rely only upon case-control comparisons and abnormality identification in characterizing a circuit and its role in a disorder. Instead, this approach must be complemented by a simultaneous assessment of how individual variability in circuit characteristics relate to variation in the symptom, process, or outcome of interest. Once specific group-level relationships between a circuit, information-processing, and/or clinical characteristic can be established to inform theory and understanding, the proximal next step is to use data-driven statistical techniques such as machine learning and predictive analytics to develop individual-level biomarkers of specific symptom-promoting processes with clinical utility (Yahata et al., 2017). This effort is highly complemented by the recent explosion in "big data" analysis techniques that emphasize use of highly multi-dimensional data in predicting observed outcomes. This field of computational psychiatry relies heavily upon machine learning, a theory-agnostic, data-driven technique that can be used for predicting diagnosis, severity, treatment outcome, or treatment assignment (Huys et al., 2016). Such data-driven methods are useful in a number of ways. First, multidimensional data can be reduced to more basic and computationally-tractable dimensions based on data-driven methods, thus allowing for the separation of heterogeneous clinical groups into more clinically or mechanistically meaningful subtypes or symptom dimensions absent of any pre-imposed theoretical structure (Brodersen et al., 2014; Drysdale et al., 2017). Second, machine learning techniques can leverage large numbers of individual predictors and complex prediction methodology to improve performance (Kim et al., 2016a,b), thus enhancing explanatory power and providing candidate clinical decision-making algorithms for treatment prediction or treatment assignment to be tested for superiority to blind assignment. This approach, geared towards understanding how mechanistic processes relate to clinical heterogeneity, thus drives the reciprocal cycle of using data to inform theory and theory to better target study designs for confirmatory hypothesis testing. Ultimately, these methods will facilitate the matching of participants to the appropriate interventions (when such interventions are developed) to target specific facets of post-trauma symptomatology (see next recommendation).

5.6. Understand if and how established evidence-based treatments impact reward circuitry function to promote improvements in diminished positive affect, and refine circuit targets to be engaged by future experimental interventions

Here, it is noted that little is known regarding how evidence based treatments for PTSD exert their mechanism of therapeutic effect in general, much less for specific aspects of PTSD symptomatology (Fonzo, Goodkind et al., 2017a, 2017b). However, a clear understanding of this process is critically important to guiding intervention development and improving clinical outcomes. Given that greater levels of diminished positive affect symptoms seem to promote poorer outcomes to established trauma-focused treatments (Taylor et al., 2001), as well as the theoretical emotion processing (Foa and Kozak, 1986) and fear extinction framework (Milad et al., 2014) underlying the development and implementation of many trauma-focused interventions, the author speculates that such intervention approaches, though efficacious as a whole, will not be uniformly effective for ameliorating both the fear/anxiety-based symptoms as well as the diminished positive affect symptoms that characterize PTSD. This remains a hypothesis to be supported or refuted, but a mechanistic understanding of how improvements in either domain are belied by changes in the function of relevant neurocircuitry will be extremely valuable to defining targets for experimental therapeutics. Once targets are identified, candidate interventions can then be assessed for target engagement and symptom change, thus providing an accelerated platform for mechanism-focused treatment development. In regard to diminished positive affect, there have been no investigations, to the author's knowledge, that have assessed reward processing behavior and neurocircuit function before and after delivery of an established PTSD intervention. This remains an area in dire need of future scientific development.

5.7. Integrate experimentally informed conceptual models of trauma effects on positive and negative valence systems into a unified framework

Ultimately, no useful brain-based affective model of post-trauma psychopathology would eschew a bivalent characterization of circuitry, symptoms, and their direct interactions. In the author's humble opinion, this remains the "holy grail" of affective neuroscience research in trauma. Specifically, that is, understanding how exaggerated negative affect and diminished positive affect are dictated by the interactions of neurocircuitry and how these interactions underlie the specific manifestation of symptoms in each domain would provide an unprecedented degree of comprehensiveness in our characterization. Moreover, as was cleverly hypothesized nearly a decade ago (Stein and Paulus, 2009), correcting this imbalance in approach and avoidance neurocircuitry may hold great promise in developing and implementing the most universally efficacious trauma intervention. The author speculates that the great success of methylenedioxymethamphetamine (MDMA)-assisted psychotherapy in promoting recovery from PTSD in treatment-resistant individuals (Amoroso and Workman, 2016) lies in its capacity for both attenuating function of threat-related circuitry as well as enhancing function of the reward circuit (Bedi et al., 2009). Future studies investigating this hypothesis would greatly benefit our understanding of how the dynamic interplay of positive and negative valence brain systems dictate the pathophysiology, manifestation, and resolution of PTSD.

6. Conclusion

In summary, the study of diminished positive affect in PTSD is currently in its early stages of development, but the field has nonetheless benefitted from the current body of work that demonstrates abnormal function of reward neurocircuitry and preliminary evidence for relationships with diminished positive affect symptoms. Much more work is needed in this area, and it remains, in the author's opinion, an underrepresented area of study in the trauma neuroscience field. Future efforts focused on dissecting components of reward processing behavior using diverse and generalizable stimuli, computational characterization of information processing functions in relevant neurocircuitry, and laboratory studies combined with ecologically valid, complementary forms of assessment will greatly enhance efforts at identifying biomarkers, defining novel bio-behavioral treatment targets for intervention development, and promoting an integrated bivalent conceptualization of a trauma's impact on the affective circuitry dictating healthy socio-emotional functioning. This joint brain-based conceptualization of negative and positive affect disturbance following trauma may hold the key to ushering in a "golden age" of effective treatments.

Acknowledgments

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ynstr.2018.10.002.

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