



## Review article

## The role of brain reward pathways in stress resilience and health

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## ABSTRACT

While it is well established that stress can increase risk for a broad range of health and disease outcomes (e.g., major depression, cardiovascular disease), less is known about factors supporting resilience. An emerging literature indicates that activation of the brain's reward system can mitigate subsequent stress responses to a broad range of stressors in animals and humans, suggesting reward pathways as a novel mechanistic target for fostering resilience under stress. This perspective will: 1) describe the emerging evidence linking primary and secondary rewards with stress buffering effects; 2) identify plausible neurobiological mechanisms; and 3) introduce new links between brain reward activation and reduced stress-related health and disease outcomes. We conclude with a discussion of research opportunities and clinical implications of brain reward effects.

## 1. The role of brain reward pathways for stress resilience and health

Although stress is related to increased health risks such as major depressive disorder and post-traumatic stress disorder (Cohen et al., 2007; McEwen, 2004), most individuals are remarkably resilient (Bonanno, 2004). Resilience is defined as the capacity to adapt successfully to acute stress, trauma, or chronic adversity (Feder et al., 2009). Despite significant public interest in this area, we still know little about the neurobiological and behavioral mechanisms of resilience (Bonanno et al., 2011; Rutter, 1985). While large independent literatures have studied the brain's reward and stress systems (Arnsten, 2009; Baxter and Murray, 2002; Berridge and Robinson, 2003; Eisenberger and Lieberman, 2004; Haber, 2011; Haber and Knutson, 2010; Herman et al., 2005; Ulrich-Lai and Herman, 2009), new research over the last ten years suggests a critical role for the brain's reward system in modulating the fight-or-flight stress response in ways that confer stress resilience. We have organized this perspective into sections that describe: 1) experimental work that demonstrates robust relationships between reward system activation and stress resilience (in animal and human models); 2) plausible neurobiological mechanisms for these effects; and 3) promising links between reward system activation and stress-related health benefits.

## 2. Activating the reward system reduces stress physiology and behavior: experimental evidence

An organism's survival depends on the ability to seek out and approach rewarding stimuli in the environment. Primary rewards are those that immediately influence survival, such as food and reproduction, whereas secondary rewards are those that may not directly impact survival but facilitate these survival behaviors, including money and positive social experiences (Berridge and Robinson, 2003; Schultz, 2015; Sescousse et al., 2013). Also key to survival is being able to successfully avoid or manage actual or perceived threats and stressors (LeDoux and Daw, 2018; Sapolsky, 2004). These behaviors are fundamental and are subserved by the brain's reward and stress systems, respectively. While these neurobiological systems are well-characterized, the relationship and interactions between them have received far less research attention. However, there is compelling experimental evidence in animals and humans showing that reward manipulations and rewarding environments foster stress resilience (see Table 1).

Administering primary rewards or providing rewarding environments reliably blunts stress reactivity responses. In humans, brief exposure to a reward stimulus (e.g., erotic images) buffered subsequent cortisol reactivity and improved problem-solving performance under stress (Creswell et al., 2013a, 2013b). Likewise, young rats given a sweet drink demonstrated greater pain tolerance and reduced distress to a social isolation stressor (Blass et al., 1987; Blass and Shide, 1994). (Interestingly, in clinical practice human infants are sometimes given a sweet drink to buffer distress to painful medical procedures (Abad et al.,

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**Table 1**  
 Experimental studies demonstrating the effect of rewarding manipulations on stress responding (physiological, affective or behavioral outcomes). Reward duration column refers to how long reward was experimentally manipulated, with acute meaning one instance. Direction of arrow indicates direction of effect on stress outcome listed compared to a relevant control condition.

Study	Model or Population	Reward Stimulus or Activation Method	Reward Duration	Primary or Secondary Reward	Stress Induction Paradigm	Stress Outcome	Direction of Effect
<b>Physiology</b>							
Ulrich-Lai et al., 2010	Male Rats	Sweet drinks	2 weeks	Primary	Restraint Stress	ACTH Corticosterone Heart rate	↓ ↓ ↓
		Sexually receptive mate	2 weeks	Primary	Restraint Stress	ACTH Corticosterone Heart rate	↓ ↓ ↓
Ulrich-Lai et al., 2007	Male Rats	Sweet drinks	2 weeks	Primary	Restraint Stress	Corticosterone	↓
Christiansen et al., 2011	Male Rats	Sweet drinks	2 weeks	Primary	Restraint Stress at: 1, 6 and 21 days after reward	Corticosterone 1 day Corticosterone 6 day Corticosterone 21 day	↓ ↓ ↓
Creswell et al., 2013a, 2013b	Human males	Erotic images	Acute	Primary	Trier Social Stress Test	Cortisol	↓
Creswell et al., 2005	Humans	Self-affirmation	Acute	Secondary	Trier Social Stress Test	Cortisol	↓
Sherman et al., 2009	College Students	Self-affirmation	Acute	Secondary	Exam Stress	Catecholamines (epinephrine and norepinephrine)	↓
Spicer et al., 2016	Humans	Self-affirmation	Acute	Secondary	Trier Social Stress Test	Endothelial cell-derived microparticles (EMPs)	↓
Speer and Delgado, 2017	Humans	Positive Memories	Acute	Secondary	Social evaluative cold pressor task	Cortisol	↓
Kirschbaum et al., 1995	Humans	Receiving Social Support	Acute	Secondary	Trier Social Stress Test	Cortisol	↓ (men) None (women)
Thorsteinsson et al., 1998	Humans	Receiving Social Support	Acute	Secondary	Demanding Computer Task	Cortisol	↓
Schwilling et al., 2015	Preterm Infants	Music	Acute	Secondary	Early days after birth in NICU	Heart Rate Blood Pressure Cortisol	↓ ↓ None
White, 1999	Heart attack patients	Music	Acute	Secondary	Hospitalization after heart attack	Low blood oxygen Low heart rate Apneas Heart rate Respiration rate	↓ ↓ ↓ ↓ ↓
Cruise et al., 1997	Elderly patients	Music	Acute	Secondary	During cataract surgery anesthesia procedure	Anxiety Blood pressure Anxiety	↓ ↓ None
<b>Affect or Pain</b>							
Blass and Shide, 1994	Infant rats	Sweet drinks	Acute	Primary	Social Isolation Heat pain	Distress vocalizations Pain avoidance (removing paw from heat quickly)	↓ ↓
Blass et al., 1987	Infant rats	Sweet drinks	Acute	Primary	Social Isolation Heat pain	Distress vocalizations Pain avoidance (removing paw from heat quickly)	↓ ↓
Abad et al., 1996	Preterm infant humans	Sweet solution	Acute	Primary	Arm venipuncture	Distress vocalizations (crying)	↓
Eisenberger et al., 2011	Young female adults in a relationship	View images of romantic partner	Acute	Secondary	Heat pain	Neural pain activity Subjective pain ratings	↓ ↓
Younger et al., 2010	Human adults in relationship	View images of romantic partner	Acute	Secondary	Heat pain	Neural pain activity Subjective pain ratings	↓ ↓
Phumdoung & Good, 2003	Pregnant women	Music	Acute	Secondary	Labor pain	Pain ratings Distress of Labor	↓ ↓
Ulrich-Lai et al., 2010	Rats	Sweet drinks	2 weeks	Primary	Unfamiliar conspecific Open-field and elevated plus-maze tests	Anxiously avoiding conspecific Avoiding exploratory behaviors	↓ ↓

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Table 1 (continued)

Study	Model or Population	Reward Stimulus or Activation Method	Reward Duration	Primary or Secondary Reward	Stress Induction Paradigm	Stress Outcome	Direction of Effect
Mackay et al., 2017	Young rats	Palatable foods	9 weeks	Primary	Social Defeat Exposure	Submissive behavior	↓
Manuel et al., 2015	Zebra fish	Palatable foods	2 weeks	Primary	Shock paradigm	Avoidance	↓
Creswell et al., 2013a, 2013b	Human males	Erotic images	Acute	Primary	Trier Social Stress Test	Impaired math performance	↓
Creswell et al., 2013a, 2013b	College Students	Self-affirmation	Acute	Secondary	Stressful, problem-solving task	Impaired verbal performance	↓

1996; Harrison et al., 2010).) Studies in which animals are chronically exposed to rewarding environments show similar effects as these reward administration studies. For example, two weeks of daily access to a sweet drink or a sexually receptive mate led to significantly lower adrenocorticotrophic hormone (ACTH), corticosterone secretion and lower heart rate to a subsequent restraint stressor challenge (Ulrich-Lai et al., 2010; Ulrich-Lai et al., 2007). Furthermore, across multiple studies, rats given regular access to rewarding food and drink also showed fewer stress behaviors, such as reduced distress vocalizations and greater exploration of novel environments (MacKay et al., 2017; Ulrich-Lai et al., 2010). In another demonstration of this effect, zebra fish given rewarding food for two weeks showed less fear responding to shock than control fish (Manuel et al., 2015). These initial reward studies have also helped identify critical neurobiological pathways for reward-stress resilience effects. Rewarded rats with a bilateral lesion to the basolateral amygdala (BLA) no longer showed stress resilience, suggesting that BLA may be a central neural processing region for reward-stress modulation (Ulrich-Lai et al., 2010). Indeed, rewarding stimuli have been shown to lead to increased plasticity in BLA and the nucleus accumbens in rats, and these changes in plasticity are associated with prolonged HPA dampening (Christiansen et al., 2011; Ulrich-Lai et al., 2010). Across species, primary rewards lead to reductions in stress as measured by multiple stress outcomes including physiological stress responding, distress to pain, and stress behaviors.

While much of the initial research has focused on the stress buffering effects of primary rewards, secondary rewards show similar effects (see Table 1). For example, human neuroimaging studies have shown that thinking about one's personal values increases reward-related neural activity in the VS (Cascio et al., 2016; Dutcher et al., 2016) and buffers cortisol, catecholamine and behavioral responses to stress (Creswell et al., 2013a, 2013b; Creswell et al., 2005; Sherman et al., 2009; Spicer et al., 2016). Thinking about positive autobiographical memories also leads to increased VS activity (Speer et al., 2014), and lowered cortisol reactivity to a stressor (Speer and Delgado, 2017). Similarly, both perceiving and receiving social support activate the VS and VMPFC (Eisenberger et al., 2011; Inagaki and Eisenberger, 2012; Younger et al., 2010), and buffer cortisol stress responding and neural markers of distress under threatening or painful conditions (Eisenberger et al., 2011; Kirschbaum et al., 1995; Thorsteinsson et al., 1998; Younger et al., 2010).

Pharmacological studies also highlight the role that reward system neurotransmitters, such as dopamine and endogenous opioids, play in stress resilience. Dopamine is known to foster stress resistance, as mesocortical release has been shown to prevent exaggerated behavioral and physiological stress reactivity and is associated with active coping to stressful events (Cabib and Puglisi-Allegra, 2012; Sullivan, 2004). Endogenous opioids have also been theorized to play a critical role in stress modulation via their influence on neuroendocrine and autonomic cascades, and behavior (Drolet et al., 2001). Endogenous opioids are also involved in blunting the distress of pain and are widely distributed through the limbic system (including the amygdala and hypothalamus), leading some to argue that opioids may attenuate physiological responses to emotional or affective states, thus lessening the impact of stress (Drolet et al., 2001).

Because dopamine and opioids are critical neurotransmitters in the reward system, and rewarding stimuli can buffer against stress, then blocking these key neurotransmitters should diminish stress resilience effects. Indeed, rats administered a dopamine antagonist, which blocks the neurotransmitter cascade from the reward system, showed increased physiological stress responding (Sullivan and Dufresne, 2006). Additionally, blocking opioids with an antagonist led to increased stress vocalization responding in cats during restraint stress (Abercrombie and Jacobs, 1988) and rats experiencing social isolation (Kehoe and Blass, 1986). Furthermore, while rewards have been shown to decrease pain sensitivity and behavioral stress responding, these effects are reversible with the administration of an opioid antagonist (Blass et al.,

1987; Forsberg et al., 1987). Consistent with a role of opioids in stress regulation, administration of an opioid (morphine) to socially isolated young rats led to decreased distress vocalizations and increased analgesic effects, whereas administration of an opioid antagonist resulted in greater stress behaviors (Kehoe and Blass, 1986). In concert, these findings suggest that dopamine and opioids play a critical role in the stress buffering effect of rewarding stimuli, and blockade increases stress responding. Future translational work could test this mechanism in human blockade studies (with antagonists such as naltrexone).

### 3. Plausible neurobiological relationships between reward and stress resilience

The reward system is a well-characterized network of regions across the limbic, prefrontal, striatal and midbrain regions (Haber and Knutson, 2010), and neural activity in these regions is relatively consistent across primary and secondary reward types, as shown in a thoughtful review of this work (Sescousse et al., 2013). Like the reward system, the neurobiology of the brain's fight-or-flight stress response system is well-characterized including regions in limbic, midbrain and prefrontal systems that mediate physiological stress responding via the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system (López et al., 1999; McEwen, 2007; Sinha et al., 2004; Ulrich-Lai and Herman, 2009). These key neural regions are in close proximity (see Fig. 1) but are functionally distinct. However, these regions also have significant connectivity, and these communication channels are the key drivers of the reward stress resilience response.

#### 3.1. Overlapping but distinct neuroanatomy for reward activation and stress responses.

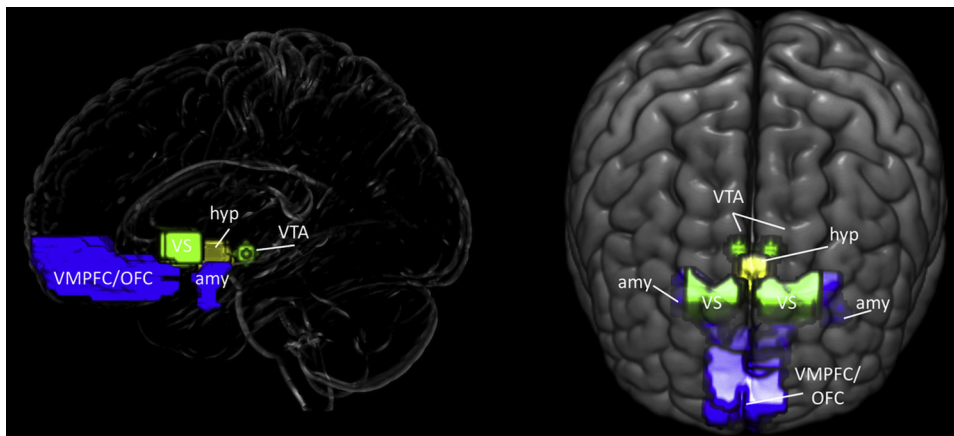
While both the stress and reward systems in the brain include limbic, prefrontal, and midbrain structures, our perspective is that there is functional specificity and segregation in these structures supporting reward and stress processes. Indeed, research in animals has identified dissociable divisions between the brain's reward and stress systems. Two important limbic regions, the hypothalamus and the amygdala, demonstrate this division. In particular, the paraventricular nucleus of the hypothalamus and the dorsomedial hypothalamus have been identified as key locations for autonomic and HPA modulation, both to activate or inhibit stress responding (Ulrich-Lai and Herman, 2009). Meanwhile, the lateral hypothalamus has been linked to reward and motivation, including reward preferences and reward seeking (Harris et al., 2005). Similarly, the central nucleus of the amygdala is thought to be most sensitive to homeostatic and systemic stressors, and is involved in autonomic responses to stress, (Ulrich-Lai and Herman, 2009) while the medial and basolateral amygdala (BLA) nuclei are activated to psychological stressors and are associated with HPA stress

responding (Ulrich-Lai and Herman, 2009). Animal studies have also implicated BLA activity in reward processing, (Baxter and Murray, 2002) (human neuroimaging results have been less clear, suggesting that human amygdala responses to reward are more about salience than value (Zald, 2003)). Furthermore, although the prefrontal cortex's cytoarchitecture does not clearly delineate specific structures, there is evidence that reward and stress responding depend on different subsections within this region. In rodent research, the prelimbic PFC (BA 32) has been shown to inhibit and regulate the HPA axis response to stressors, whereas the infralimbic PFC (BA 25) seems to initiate HPA response to stress (Radley et al., 2006). (To extend to human anatomy, the prelimbic PFC is most like the dorsal VMPFC, and the infralimbic is most like the subgenual VMPFC.) This work suggests more fully mapping these nuances in structures is a future direction for research in this area, particularly with advances in high-resolution neuroimaging in humans. Understanding more about these dissociable regions might hold promise for elucidating the mechanism by which rewarding stimuli can reduce stress responding. If these systems are separate and specific, then functional and chemical connectivity between them are the most plausible neurobiological mechanisms for stress resilience

#### 3.2. Structural, functional and neurochemical connectivity between reward and stress systems.

There are strong neurobiological pathways linking regions within the reward and stress systems. One such pathway is via plausible structural connections that could support reward-stress resilience effects. For example, limbic and forebrain reward system structures have projections to stress system regions that regulate physiological stress response cascades, like the hypothalamus and brainstem (Ulrich-Lai and Herman, 2009), resulting in decreases in HPA stress responding (Diorio et al., 1993). Specifically, the VS, and VMPFC/OFC project to the hypothalamus, while the VMPFC/OFC has direct projections to the brainstem as well (Brinley-Reed et al., 1995; Haber, 2011; Haber and Knutson, 2010; Sesack et al., 1989; Terrence and Neafsey, 1987). Similarly, the VMPFC/OFC has direct projections to the amygdala (Brinley-Reed et al., 1995; Haber and Knutson, 2010), and the VS indirectly projects to the amygdala through the cholinergic fibers in the nucleus basalis in the basal forebrain (Haber and Knutson, 2010). Greater understanding of the structural connections between these systems and how they might support reward system modulation of stress responding is an exciting avenue for future research.

Importantly, in addition to these structural communication pathways, there is also evidence of functional modulation between the reward and stress systems. Human neuroimaging has also found that activating VS or VMPFC to rewarding stimuli leads to corresponding functional decreases in neural and behavioral responses to pain stimulation (Eisenberger et al., 2011; Younger et al., 2010). In the context



**Fig. 1.** Figure displaying locations of key brain regions within reward and stress systems on two different orientations of the brain.

The VS is a collection of regions within the basal ganglia including the caudate nucleus, caudate head, nucleus accumbens (NAcc), and ventral portions of the putamen (Haber, 2011). The VMPFC and OFC are often labeled interchangeably depending on the author and animal model being studied.

VS = ventral striatum; amy = amygdala; VMPFC = ventromedial prefrontal cortex; OFC = orbitofrontal cortex; hyp = hypothalamus; VTA = ventral tegmental area.

of fear, functional interactions between the ventral striatum and the amygdala are associated with coping with and learning to avoid fear (Delgado et al., 2009). Negative affective stimuli are associated with increased amygdala activity, and activity in the VMPFC has been shown to be inversely correlated with this amygdala activity (Banks et al., 2007; Kim et al., 2003; Urry et al., 2006); additionally, the stronger the inverse coupling, the greater the declines in cortisol secretion (Urry et al., 2006). These results suggest that beyond the structural connections between reward and stress systems, there is evidence of functional modulation in line with this account as well.

For a number of years, theorists have suggested that opioids regulate pain and fear responses to enhance survival by giving the organism a chance to respond to the threat (Fanselow, 1986; Fields, 2006; Leknes and Tracey, 2008). Here, we suggest that this same potential opioid regulation mechanism might be one mechanism by which rewarding stimuli can reduce stress responding. Indeed, blocking opioids reverses the effect of rewards on distress vocalizations in cats and rats (Abercrombie and Jacobs, 1988; Kehoe and Blass, 1986). Importantly, although the opioid antagonist (naltrexone) is a nonspecific receptor antagonist, there is evidence that it is preferential for mu opioid receptors (Raynor et al., 1994; Wang et al., 2001), highlighting the possibility that mu opioids are a key neurotransmitter for the effects of reward on stress responding. Indeed, of the three primary opioid receptors, the mu receptor is the one most expressed in the amygdala, a critical structure for stress regulation, and mu opioids are implicated in reward processing of a variety of different rewarding stimuli (Le Merrer et al., 2009).

Dopamine is a well-established reward system neurotransmitter, with dopamine neurons residing throughout regions within the mid-brain including the VTA and VS, and rewarding stimuli leading to dopamine release (Haber and Knutson, 2010). Interestingly, blocking dopamine has been shown to increase stress (Sullivan and Dufresne, 2006), and dopamine administered directly to the central nucleus of the amygdala led to attenuation of stress-induced ulcer formation (Ray et al., 1987), suggesting a role for dopamine in stress regulation. However, the role that dopamine plays in stress reduction is not clear. For example, animal work has also demonstrated dopamine release in the presence of a stressor (Abercrombie et al., 1989). Some theorize that dopamine in the reward system leads to stress adaptation, such that it does not always facilitate stress nor reduce stress, but rather that it serves as a critical feedback mechanism to prevent exaggerated stress responses (Cabib and Puglisi-Allegra, 2012; Sullivan and Dufresne, 2006). Greater research is needed to understand the role, if any, that dopamine plays in reward-stress effects.

The last two decades have seen an increased interest in oxytocin and the role that this neuropeptide may play in behavior (cf. Yoshida et al., 2009). For example, work has demonstrated that central administration of oxytocin in rats leads to reduced behavioral and physiological responses to stress (Windle et al., 1997). Furthermore, some work in humans has suggested that social rewards and the stress buffering effect may interact with or depend upon oxytocin (Chen et al., 2011; Dölen et al., 2013), suggesting that oxytocin is a possible substrate for reward's effects on stress buffering. However, other work demonstrates that oxytocin can decrease the rewarding effects of dopamine (Baracz and Cornish, 2013). While oxytocin can lead to enhanced positive or prosocial behavior under certain conditions, work has also found that oxytocin leads to enhanced negative behaviors when individuals feel unsafe or stressed, highlighting the complexity of oxytocin's role in behavior (Olf et al., 2013). Oxytocin receptors are present in many stress and reward-relevant brain structures (amygdala, striatum, hippocampus and brainstem), but their precise effects on stress physiology is mixed; in fact, oxytocin can also promote cortisol release (Meyer-Lindenberg et al., 2011). Thus, oxytocin may be an important moderator (but not a mechanism) of reward-stress interactions via its interactive role with the dopamine and opioid systems (Onaka et al., 2012; Strathearn, 2011; Tops et al., 2014). Indeed, work in this area

suggests that oxytocin may influence corticostriatal reward systems via these neurotransmitter mechanisms to lead to resilience to stress (Tops et al., 2014). However, the interactions between oxytocin and the reward-stress buffering effect are an important candidate for future research.

In summary, there is significant structural connectivity within and between reward and stress regions, and functional associations that support inhibition between the reward system and the stress system. Additionally, we believe opioids (mu opioids in particular) serve as an important chemical conduit for this stress resilience effect. While examining the neurobiological communication mechanisms between these two systems is still in its infancy, the evidence thus far demonstrates links that support interaction between the two systems, in ways that could allow the animal or organism to adaptively respond to aversive threats (Leknes and Tracey, 2008).

#### 4. Reward-stress resilience pathways: implications for health

If brain reward pathways confer stress resilience, one implication is that they could protect against stress-related health outcomes. It is well-established that stress can trigger the onset and exacerbation of a broad range of psychiatric disorders (e.g., depression, PTSD, addictive disorders) and physical health conditions (e.g., cardiovascular disease, cancer) (Cohen et al., 2007; Hammen, 2005; Jones and Barlow, 1990; McEwen, 2004; McEwen and Gianaros, 2010; Sinha, 2008). Despite the promise of a reward-stress resilience-health link, there is surprisingly little work investigating how manipulating or intervening upon reward processes might affect health and disease (cf. Cascio et al., 2016; Falk et al., 2015). Correlational work has found that engaging in rewarding activities is associated with stress reduction and health benefits (e.g., lower depressive symptomatology, lower blood pressure) (Pressman et al., 2009). Furthermore, enriched environments have similar benefits in rodents, including decreased physiological and behavioral stress responding, and increased innate immunity (Belz et al., 2003; Benaroya-Milshtein et al., 2004; Carlstead and Shepherdson, 2000; Francis et al., 2002). However, recent work has leveraged the current understanding in neuroscience to explore associations between the reward system and health.

Experimental studies with animals have begun to explore the role of the reward system in physical health. For example, in rats, a dopamine agonist or injection (into the BLA) attenuated ulcer formation following cold restraint stress, while a dopamine antagonist aggravated ulcer formation (Ray and Henke, 1991). Additionally, the development of new transgenic mouse models has been used for evaluating the role the reward system plays in health. Specifically, researchers have used a Designer Receptors Exclusively Activated by Designer Drugs model (DREADDs) (Ben-Shaanan et al., 2017) to directly activate endogenous dopamine neurons within the mouse VTA, and then exposed the mice to a bacterial challenge. Findings indicate that activating the VTA led to an increase in innate and adaptive immune responses to the bacterial challenge (Ben-Shaanan et al., 2016). While the DREADDs work is newer, it is likely to be an important method for exploring many other relationships between reward pathways and stress-mediated health risks (e.g., cancer, depression). For example, recent work using this same paradigm found that activating the VTA of tumor-bearing mice led to reductions in tumor weight via sympathetic nervous system (SNS) influences on anti-tumor immunity (Ben-Shaanan et al., 2018), linking reward system activation to a major health outcome.

Human neuroimaging studies have reported suggestive links between reward and stress-related mental health. Among individuals who reported experiencing significant post-2016 election distress, greater VS (NAcc) activity to a rewarding task was associated with fewer depressive symptoms, diminishing the relationship between election distress and depression (Tashjian and Galván, 2018). A similar effect was demonstrated with adolescents, showing that greater reward-related neural activity to eudaimonic rewarding stimuli was associated with

longitudinal declines in depressive symptoms (Telzer et al., 2014). These studies are correlational and more experimental work is needed, including work exploring how rewarding interventions affect stress-related mental health outcomes (e.g., depression, substance abuse) (Hammen, 2005; Sinha, 2001).

#### 4.1. Absence or Loss of Reward and Health

While we have spent the majority of this review discussing the impact that anticipating or receiving a reward might have on reducing stress responding and the implications for health. However, there is literature that suggests that anticipating a reward but then having that reward revoked or withheld leads to increased activity in regions of the brain's stress system and a corresponding decrease in reward system activation (Abler et al., 2005; Hernandez Lallement et al., 2013). Thus, it seems likely that while the anticipation of reward leads to activation of the reward system, having that reward stimulus taken away is not only *not* rewarding, it seems to be its own stressor. This would counteract the brief activation of reward pathways and ultimately lead to increased, rather than decreased, stress responding. Indeed, work on Effort-Reward Imbalance (Siegrist, 1996) suggests that high stress and low reward circumstances at work and in relationships have potent negative health effects (Dragano et al., 2017; Rugulies et al., 2017; Sperlich et al., 2012; von dem Knesebeck and Siegrist, 2003). Taken together, these literatures suggest that the loss or absence of rewarding stimuli and environments is stress exacerbating and has negative health consequences. However, to our knowledge, work has not yet examined the neural underpinnings of this loss of reward-stress exacerbating effect on health or markers of health, which could help clarify how these two neural systems communicate under these low-reward circumstances.

The impact that reward-stress buffering has on health outcomes is a very new area of study, and the links we have detailed here are merely suggestive. Furthermore, across human and animal studies, most have not yet explored both how rewarding stimuli could reduce stress responding and how this effect could improve health in the same study. The literature finds that reducing stress can have important implications for health outcomes (Creswell and Lindsay, 2014; Haslam et al., 2016; Tetrick and Winslow, 2015; Wagner et al., 2016), but only a few studies have pointed to reward processing as a possible correlate for health (Ben-Shaanan et al., 2016, 2018; Telzer et al., 2014). But future work can help establish whether the reward-stress buffering account we have laid out here serves as a mechanism for stress resilience effects on health.

### 5. Discussion and future directions

Large independent literatures have focused on the reward and stress systems, yet much less attention has been paid to how these systems interact. Here, we describe exciting new research linking reward system activation with stress resilience, as well as initial links to stress-related health outcomes. We reviewed a range of human and animal studies linking reward system activation (and rewarding environments) with stress resilience effects (see Table 1). Consistent with this reward-stress account, reward-related neurotransmitters play a critical role in driving stress resilience effects in pharmacologic studies, and one goal of this perspective was to outline some plausible neurobiological pathways linking the reward system with stress resilience. For example, reward regions such as the VS and VMPFC have been shown to have structural and functional inhibitory connections to regions that deploy the physiological stress response. Empirical evidence in animals also points to endogenous opioids as a critical neurobiological communication pathway for reward mediated stress reduction. Future human studies can capitalize on advanced, high-resolution neuroimaging and pharmacological blockade protocols to supplement the animal findings in support of these connections. In sum, the work we have summarized

here synthesizes the human and animal work demonstrating a reliable and consistent reward-stress reduction pattern, while highlighting the connectivity between the reward and stress systems that could support this effect. While some accounts have suggested significant overlap between the neurobiology, our perspective, informed by animal studies, is that this overlap is more nuanced, and we hope this catalyzes further research in this area.

This reward-stress buffering work carries potential implications for stress-related disorders and health outcomes. Although this research area is still young, there are a few demonstrations with pharmacological manipulations in rats, transgenic mouse models, and cross-sectional mental health studies in humans (Ben-Shaanan et al., 2016; Ray and Henke, 1991; Tashjian and Galván, 2018; Telzer et al., 2014). These studies suggest that activating the reward system might reduce the risk of stress-related health problems, boost immunity and reduce the risk of depression (Ben-Shaanan et al., 2017; Tashjian and Galván, 2018; Telzer et al., 2014). But more prospective randomized controlled trials are needed to test these stress resilience-health links.

There is still quite a bit to learn about the pathways linking reward system activation and stress resilience. First, greater understanding of the anatomical and functional connections between neural regions involved in reward and stress processing would buttress the current body of behavioral research in this area. In humans, diffusion-tensor imaging (DTI) and diffusion-spectrum imaging (DSI) continue to improve as techniques for mapping the white matter tracts within these neural circuits, which will help provide a better understanding of the interactions between the brain's reward and stress response systems. Second, future research can also help clarify the signaling pathways that confer resilience. The initial evidence in this area has focused on neurotransmitter antagonist administration studies in animals, but these antagonists have analogs that could be used in translational studies with humans. Careful work with important novel methods will be important for establishing the precise roles that opioids and dopamine have in modulating stress responding.

The perspective we have described, and the evidence to date, shows that a broad range of rewards, from sweet substances to thinking about important values, can have stress buffering effects. However, the timing, duration, and category of reward could influence stress resilience and we still know little about the boundary and moderating effects of these factors. But as an example, recent human neuroimaging work in adolescents shows that reward-related neural activity to eudaimonic rewarding stimuli—prosocial decisions—was associated with declines in depressive symptoms over time, while reward-related neural activity to hedonic rewarding stimuli—decisions that were more self-ish—was associated with increases in depressive symptoms over time (Telzer et al., 2014). Importantly, this work does not suggest that these rewarding stimuli did not both buffer against stress responding (that was not tested in this experiment), but it suggests that future work directly comparing different types of rewards' effects on stress responding might identify the specific contexts that lead to health benefits. Furthermore, while both primary and secondary rewards may have similar stress resilience benefits, in clinical practice they may have different long-term consequences. For example, eating a rewarding food prior to a stressful event may lead to consumption of excess calories, whereas thinking about a positive autobiographical memory may have the rewarding benefits without the calories.

While we described evidence for the effect of reward manipulations on stress buffering, how long these effects persist is not clear. However, there is some initial evidence suggesting that these effects may have persistent effects. Specifically, stress resilience effects have been observed in rats 21 days after the last rewarding food stimulus (Christiansen et al., 2011). Moreover, greater frequency and longer duration of reward administration has been shown to lead to greater HPA dampening, but increased volume or amount of reward did not (Ulrich-Lai et al., 2011). Taken together, these findings suggest that frequent rewarding experiences might have lasting impacts on

biological stress responding and identify two important directions for future research: 1) understanding the timing and duration for when rewarding stimuli might be most effective in reducing stress, and 2) investigating how rewarding stimuli might alter stress systems, as it is possible that short-term interventions that activate the reward system have longer-term effects on stress-related outcomes via stress system plasticity. We know that chronic stress has potent negative effects on health (Cohen et al., 2012; Mcewen, 2004), and thus it will be important to understand the effects of long-term rewarding environments for those facing chronic stress as well.

The majority of the research we reviewed manipulated reward via direct reward administration (e.g., consuming a sweet drink or thinking about one's values). In some cases, the animals were given access to a rewarding stimulus for a period of time—making it difficult to isolate whether these effects are due to the pleasurable experience of the stimulus, the anticipation of the stimulus, or a general activation of the reward system. The anticipation of reward activates the reward system as much as the receipt of reward (Berridge and Robinson, 2003; O'Doherty et al., 2002), so we speculate that both receiving or anticipating a reward may be sufficient for facilitating stress resilience effects, although more research is needed to test this hypothesis.

While the present body of work suggests that rewarding activities could be a tool for buffering anticipated stressful events, there are still many open questions about the translational value of reward-stress interactions for clinical contexts. For example, reward manipulations could help lessen stress responding in triggering contexts among anxiety and panic disorder patients. Yet it is not clear whether reward pathways can be stimulated to buffer against chronic unrelenting forms of stress (e.g., caregiving, chronic illness). But as previously described, there is some promising initial indication in epidemiological work that rewarding activities are associated with reductions in stress, depressive symptomatology, and blood pressure among individuals dealing with longer-term stressors (Pressman et al., 2009). Finally, this perspective on reward-stress resilience effects may have utility for understanding other therapeutic approaches. Reward pathways may be a common underlying mechanism linking a broad range of evidence-based behavioral treatments with stress resilience (e.g., cognitive-behavioral therapy, mindfulness training).

## 6. Conclusions

The findings presented here suggest that reward system activation can reduce behavioral and physiological responses to stress in both human and animal models. Neural, behavioral, and pharmacological studies support the neurobiological plausibility for reward-stress resilience effects, highlighting the role of connectivity between reward structures (such as VS and VMPFC) and structures that initiate physiological stress responding (hypothalamus and amygdala), as well as the role of opioids in this relationship. These findings, and this account, highlight new directions for building out mechanistic research and translational interventions linking rewards, stress resilience, and health outcomes in health neuroscience.

## Author contributions

Both authors conceptualized and wrote the paper.

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