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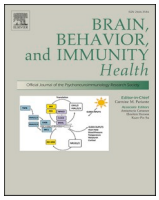

Neural and immune interactions linking early life stress and anhedonia

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A R T I C L E I N F O

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A B S T R A C T

Early experiences of stress and adversity are associated with blunted reward sensitivity and altered reward learning. Meanwhile, anhedonia is characterized by impairments in reward processing, including motivation, effort, and pleasure. Early life stress (ELS) and anhedonia share psychological, behavioral, and neurobiological correlates, and the system-level interactions that give rise to anhedonia have yet to be fully appreciated. The proposed framework uses a multilevel, multisystem approach to aid in understanding neural-immune interactions that link ELS and anhedonia. The interactions linking anhedonia and ELS presented here include reduced reward sensitivity, alterations in hypothalamic-pituitary-adrenal (HPA) axis response, elevated inflammatory cytokines or physiological markers of stress, and blunted reward circuitry functioning along the mesocorticolimbic pathway. The clinical implications and areas for future research are also discussed. Ultimately, this research may inform the development of more specific and individualized treatments for anhedonia.

1. Introduction

As a transdiagnostic symptom across psychiatric and neurological conditions (APA, 2013; Insel et al., 2010; Trøstheim et al., 2020), anhedonia often precedes diagnosis (Wardenaar et al., 2012), and is associated with a more chronic course (Gabbay et al., 2013). As a hallmark symptom of major depressive disorder (MDD), anhedonia significantly predicts depressive severity and suicidality in adolescence (Gabbay et al., 2015). Models of internalizing psychopathology theorize that anhedonia is reflective of low positive affect (Clark and Watson, 1991), social withdrawal, and high behavioral inhibition (Laptook et al., 2008), or an inability to orient toward rewards. Importantly, remission of MDD co-occurs with the restoration of positive affect, highlighting the clinical relevance of anhedonia and its distinction from low mood (Zimmerman et al., 2006). Traditionally defined as the inability to experience pleasure, or reduced hedonic capacity (Meehl, 1975), anhedonia is more recently operationalized as a "transdiagnostic correlate of internalizing conditions" (Conway et al., 2019), characterized by impairments in one or more subtypes of reward processing, including motivation, effort, and pleasure (Berridge and Kringelbach, 2008; Borsini et al., 2020; Treadway and Zald, 2011). Moreover, trait anhedonia is endorsed by individuals without psychiatric disorders (Keller et al., 2013), further suggesting that anhedonia is not specific to any condition and can be considered an inherent trait.

A critical gap remains in understanding how individual differences in reward processing that are shaped in early development may contribute to anhedonia, or reduced reward sensitivity and reward learning. Individual differences in affect and reward processing are believed to be shaped by early experiences of stress and adversity (Pizzagalli, 2014). Early life environments characterized by lower responsiveness from caregivers and lower positive emotions tend to reduce sensitivity to positive stimuli (Smith and Pollak, 2020). Importantly, approximately 30–60% of the U.S. population reports exposure to early life stress (ELS) (Green et al., 2010; Merrick et al., 2018), according to surveys on adverse childhood experiences (ACE's) such as neglect, abuse, extreme poverty, domestic or community violence, and separation. Specific stressors in early life may exceed a child's coping resources, and there is increasing recognition that long-lasting sequelae from physical, emotional, and sexual abuse, as well as familial mental health, substance use, and legal problems, serve as risk factors for psychiatric illnesses and diseases (Berens et al., 2017; Danese and Lewis, 2017; Herzberg and Gunnar, 2020; Smith and Pollak, 2020).

The likelihood that an individual who experiences stress or adversity goes on to develop adverse physical or mental health conditions is greater when neural and immune systems are impacted; that is, when stress "gets under the skin" (Dennison et al., 2019; McEwen, 2012; Taylor, 2010). Dimensional models of ELS recognize that different types of stressors may lead to unique outcomes (Sheridan and McLaughlin, 2014), though different types of ELS appear equally likely to sensitize neural and immune systems (McMullin et al., 2020; Nusslock and Miller, 2016). The stress sensitization model of anhedonia, proposed here, highlights how stressors influence neural and immune system

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development (Boyle et al., 2023; Hostinar et al., 2015; Young et al., 2018). The current review integrates literature on interactions between neural and immune systems that are critical for both reward seeking and maintaining equilibrium between positive and negative affective states, and introduces a framework to describe the putative affective, behavioral, and neurobiological mechanisms between ELS and anhedonia (Fig. 1). The proposed framework uses a multilevel, multisystem approach to aid in understanding neural-immune interactions that link ELS and anhedonia. The neural-immune interactions presented here include reduced reward sensitivity, alterations in hypothalamic-pituitary-adrenal (HPA) axis response, elevated inflammatory cytokines or physiological markers of stress, and blunted reward circuitry functioning along the mesocorticolimbic pathway (Dillon et al., 2014).

2. Neural and behavioral correlates of reward response linking anhedonia and early life stress

2.1. Anhedonic phenotype following early life stress

Early life adversity shapes how children learn about and interact with their environments, and stressors are shown to result in impairments in motivation and anticipation of rewards. Reduced approach motivation following ELS is reliably demonstrated (Novick et al., 2018). Insensitivity to the expected value of reward and blunted hedonic impact also mirror individual differences in positive affect (Heininga et al., 2017). Individuals who have not been exposed to high stress and are characterized by high positive affect show increased reactivity to rewards and even "display more adaptive responses to stress" (Corral-Frías et al., 2015). In stressful environments, an individual may learn that positive emotions and other rewarding stimuli are unreliable and may be less likely to approach rewards to conserve energy (Novick et al., 2018). Anhedonia may be one direct consequence of having to expend more energy towards perceived stressors or threats in the environment, or hypervigilance following stressors.

In preclinical models of ELS, anhedonia is a reliable consequence of objective stressors and lack of control over stressors (Abramson et al., 1978). Anhedonic behavior in animals (e.g., reduced social interaction, blunted hedonic taste reactivity) is observed during various stages of reward processing (Scheggi et al., 2018). Maternal separation is perhaps the most common model for probing ELS in animals, whereby mouse pups are repeatedly separated from their dam during the first few weeks of life. This paradigm demonstrates that separation periods of 3–6 h over several days are associated with increased behavioral inhibition (Dutcher et al., 2020). Relatedly, limited bedding and nesting is a model for impoverished environments, in which maternal behavior becomes unpredictable and fragmented, reliably leading to anhedonic behavior in pups (Bolton et al., 2018; Molet et al., 2016; Walker et al., 2017). Repeated stressors in adulthood that follow ELS ("two-hit") result in worse, long-term health outcomes (Peña et al., 2017). In adult mice, social defeat stress is a preclinical model wherein a smaller and meeker mouse is repeatedly forced to intrude into the cage of a larger more aggressive mouse, resulting in dramatic social avoidance and reduced locomotion (Berton et al., 2006). Functionally, animals adapt to repeated unpredictable and uncontrollable stress by shifting to more habitual behaviors and reducing goal-directed behavior, indicative of anhedonia, thus supporting a stress-sensitization or "two-hit" model of stress (Hollon et al., 2015). One mechanism for these negative outcomes following repeated stressors may be increased permeability of the blood brain barrier. For example, following chronic social defeat stress, increased blood-brain-barrier permeability allows peripheral cytokines to "infiltrate the brain parenchyma," thereby inducing morphological changes in reward-related brain regions and contributing to behavioral inhibition (Menard et al., 2017). While these animal models are not perfect proxies for the types of chronic early life stress that humans face, they strongly support the stress-induced anhedonia paradigm.

The role of the body's stress response system is to promote adaptive functioning and mobilize physiological resources for survival (Gunnar and Quevedo, 2007); however, chronic stress incurred in early life can dysregulate this system and alter reward processing. In humans, children who have been maltreated or have endured physical abuse tend to show reduced sensitivity to rewards (Guyer et al., 2006). Maltreated youth showed poor associative learning, such that they had difficulty learning which stimuli were likely to result in reward (Hanson et al., 2017). Maltreated children tended to make inconsistent reward-related decisions that corresponded with high variability in caregiver responses.

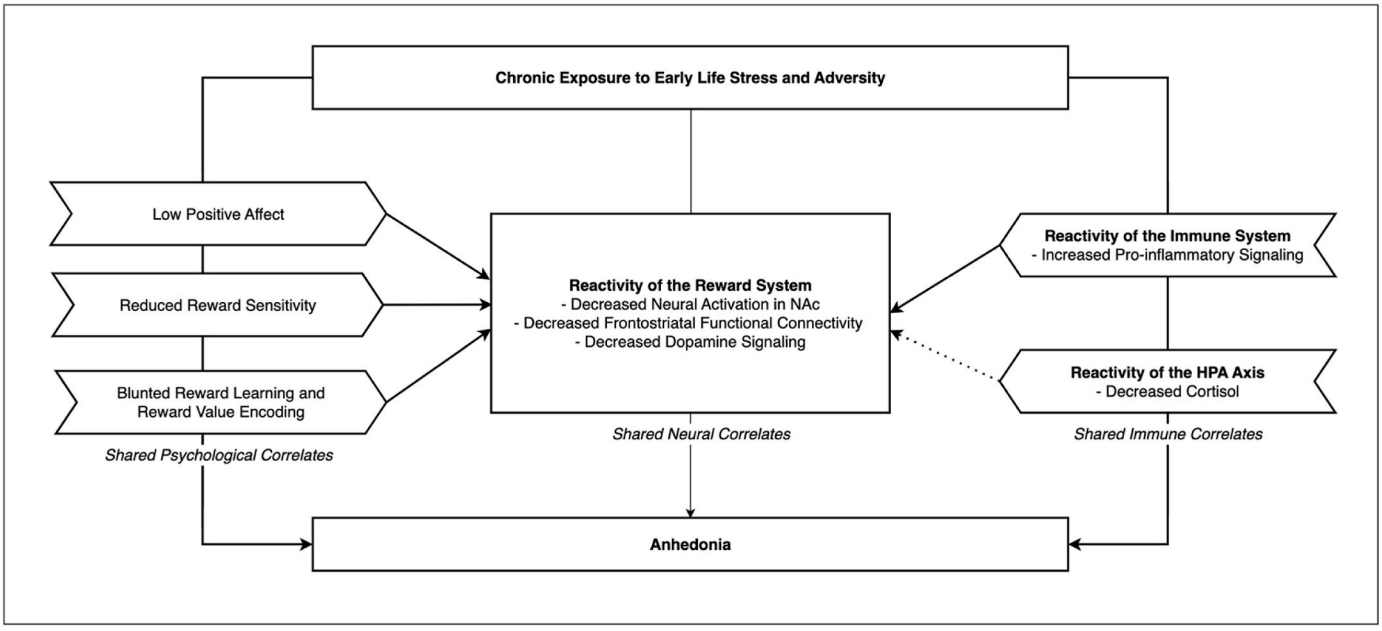

Fig. 1. Model for the sensitization of neural and immune systems linking early life stress and anhedonia. Directional arrows represent putative mechanistic pathways for shared psychological, neural, and immune correlates. The dotted pathway represents a hypothesized mechanistic pathways. HPA; Hypothalamic-pituitary-adrenal. NAc; Nucleus accumbens.

Furthermore, adults who self-report child maltreatment show blunted responses to reward cues and elevated anhedonia and depressive symptoms (Dillon et al., 2009). Taken together, early life stressors prime the brain and body toward increased threat sensitivity and decreased reward sensitivity. These effects of stress incurred during sensitive periods are thought to persist even after the stressor has been removed (Koss and Gunnar, 2018).

2.2. Neural correlates of anhedonia

Blunted neural reactivity to rewards is a neural correlate of anhedonia across psychiatric conditions (e.g., MDD, schizophrenia) (Meehl, 1975). For example, individuals who engage in rewarding activities less frequently are believed to have an "anticipatory pleasure deficit," such that they are not expecting to derive pleasure from rewarding activities (Watson and Naragon-Gainey, 2010). Accordingly, alterations along the mesocorticolimbic pathway, the brain's reward system, are consistently associated with anhedonia severity (Admon and Pizzagalli, 2015; Gabbay et al., 2013; Gradin et al., 2011). The mesocorticolimbic system passes through the reward learning (-meso), cognitive control (-cortico), and emotional (-limbic) hubs of the brain (Berridge and Robinson, 2003). The mesocorticolimbic reward system is comprised of several brain structures, namely the nucleus accumbens (NAc), caudate nucleus, putamen, ventral tegmental area, and prefrontal cortex (PFC) (Russo and Nestler, 2013). These brain regions are active during various stages of reward processing and the ventral striatum, which contains the NAc, plays a critical role in reward processing. Specifically, the NAc works to encode salience of rewarding stimuli (Borsini et al., 2020; Heshmati and Russo, 2015). Studies investigating reward circuitry functioning using functional magnetic resonance imaging have found that blunted reward-related ventral striatum activity (Ng et al., 2019; Zhang et al., 2013) and decreased corticostriatal connectivity are associated with anhedonia (Borsini et al., 2020).

2.3. Early life stress predicts reduced reward sensitivity and blunted neural reactivity

Longitudinal studies illustrate associations between childhood stress and reduced activation of cortical regions during the anticipation of potential reward losses and increased cortical activation during actual loss (Birn et al., 2017). In adolescence, lower ventral striatal (VS) activation is uniquely associated with greater emotional neglect (Hanson et al., 2015) and reduced sensitivity to rewards (Forbes and Dahl, 2012). Ventral striatal hypoactivity, specifically within the NAc, is consistently reported following ELS (Goff et al., 2013; Mehta et al., 2009) and trends longitudinally with depressive symptoms (Hanson et al., 2015). Moreover, in a study of young adults exposed to early life stress, individual differences in ventral striatal (VS) reactivity to reward were associated with increased risk for anhedonia (Corral-Frías et al., 2015). Further, in individuals who have experienced ELS, there is evidence that reward-related brain regions demonstrate altered connectivity patterns (Fareri and Tottenham, 2016). Disruption of reward circuitry following ELS is reported in both humans and preclinical models (Hanson et al., 2021). In a small adolescent sample with MDD, anhedonia severity was associated with increased intrinsic functional connectivity (FC) between striatal regions (e.g., caudate, putamen, and NAc) and cortical regions in the anterior cingulate cortex and supplementary motor area (Gabbay et al., 2013). Additionally, as these alterations in reward circuitry appear to persist into adulthood (Corral-Frías et al., 2015; Goff et al., 2013), they may be confounded by recent life stress. Together, these findings support a pathway from ELS to anhedonia via reduced sensitivity to rewards.

The magnitude of effect of ELS on neural response to rewards appears to be dependent upon the chronicity of stressors. In a large sample of young adults with exposure to self-reported maltreatment during childhood, Hanson et al. (2018) reported increased FC between the medial prefrontal cortex and left ventral striatum; however, this association was dependent on recent life stress. Recent investigations into structural connectivity of the corticostriatal circuit have also found relations between ventral striatum to frontal brain tract integrity and childhood adversity (Kennedy et al., 2021). Together, evidence supports the link between ELS, anhedonia, and blunted reward sensitivity, and the potential confounding influence of recent life stress (Birn et al., 2017).

2.4. Early life stress predicts slower reward learning and altered encoding of reward value

Early environments characterized by instability and uncertainty are especially likely to alter reward learning and value encoding (Hanson et al., 2017). High cumulative early life stress is associated with slower reward-related decision making and failure to adapt following repeated losses (Birn et al., 2017). There is preliminary evidence that altered reward learning may even persist into adulthood, as evidenced by findings of decreased positive feedback sensitivity during learning, in a sample of adults who retrospectively reported ELS (Wilkinson et al., 2021). Importantly, anhedonia is associated with greater reward prediction errors, or the gap between expected and actual outcomes, on reward learning tasks (Pizzagalli, 2022).

This observed pattern in reward learning is consistent with studies showing that stress exposure in childhood alters "how value information is used" (Smith and Pollak, 2022). Dopamine (DA) is implicated in reward learning (Berridge, 2006; Berridge and Robinson, 2016) and codes for incentive salience (Berridge and Robinson, 1998), transferring value from the reward to the cue that predicts the reward. Striatal DA release correlates with reward coding during anticipation (Borsini et al., 2020) and is linked to reward wanting, decision-making, and the perception of effort, rather than the perception of pleasure (Der-Avakian and Markou, 2012; Salamone and Correa, 2012; Treadway et al., 2012). The link between mesocorticolimbic DA functioning and reward processing is well documented; alterations in DA signaling are associated with behavioral impairments in motivation and the anticipation of rewards (Der-Avakian and Markou, 2012; Pizzagalli, 2014; Russo and Nestler, 2013). ELS may differentially impact striatal DA functioning and increase risk for anhedonia (Danese and Lewis, 2017; Smith and Pollak, 2020); however, the directional relationship between ELS and DA is less well understood.

Preclinical paradigms in animals show altered mesocorticolimbic DA functioning following stressors, but findings are not consistent with an anhedonic phenotype. For example, in isolation rearing, weaned pups are unable to interact socially or experience external stimuli (e.g., noises, light). These animal models demonstrate seemingly opposite patterns of dopaminergic functioning: hyperactivation of mesolimbic DA in the nucleus accumbens and hypoactivation of mesocortical DA in the prefrontal cortex and hippocampus (Fone and Porkess, 2008). Behaviorally, animals reared in isolation continue to engage in "food motivated learning tasks, even after satiation," which is inconsistent with an anhedonic phenotype. In humans, there is some evidence that mesolimbic DA release in response to acute stress is altered in adults who retrospectively report low parental bonding (e.g., low positive emotion and limited affection) (Pruessner et al., 2004). Further research is needed to better understand how alterations in dopamine signaling may persist following ELS to contribute to the development of anhedonia.

3. Inflammatory processes linking ELS and anhedonia

Chronic stress-induced immune dysregulation effectively decreases motivation and goal-directed behavior, two key metrics of reward sensitivity, that coincide with anhedonia and other "sickness behaviors" triggered by infection (e.g., fatigue, reduced concentration) (Ironside et al., 2018; Janicki-Deverts et al., 2007). Pro-inflammatory signaling

following stress or infection may disrupt reward-related neurocircuitry and dampen reward sensitivity (Nusslock and Miller, 2016). Research on maltreatment in early life points to dysregulated neural and immune functioning following reports of maternal rejection, exposure to harsh discipline, disruptive caregiver changes, sexual abuse, and physical abuse resulting in lasting bruising or injury (Berens et al., 2017; Herzberg and Gunnar, 2020; Kuhlman et al., 2020). In adults, experimentally-induced inflammation significantly reduces ventral striatal activity to rewards – again, a neural correlate of anhedonia (Eisenberger et al., 2010; Moieni et al., 2019). Upregulation of proinflammatory cytokines, via injection of an endotoxin, also serves to worsen depressed mood over time and induce anhedonia (Burrows et al., 2021; Eisenberger et al., 2010). Moreover, heightened inflammation is associated with decreased corticostriatial connectivity and increased anhedonia (Felger et al., 2015). Meanwhile, exposure to childhood trauma predicts heightened pro-inflammatory responses (Baumeister et al., 2016; Danese et al., 2007; Danese and Lewis, 2017; Kuhlman et al., 2023). Important work in recent years further highlights the interactive effects of ELS and early-life immune activation on heightened risk for stress-related psychopathologies, and particularly major depression (Danese and Lewis, 2017; Giollabhui et al., 2020). There are comprehensive reviews highlighting the associations between early life stress and inflammation (Dutcher et al., 2020), inflammation and altered reward circuitry (Felger, 2018), and more recently, anhedonia and inflammation (Bekhbat et al., 2022; Boyle et al., 2023; Lucido et al., 2021).

3.1. Early life stress contributes to hypothalamic-pituitary-adrenal axis hypoactivation

Research on HPA axis dysregulation following ELS indicates a pattern of reactivity that is dependent upon the chronicity of stress. Acute stressors result in hyperactivity of the HPA axis, while chronic stressors result in hypoactivity or downregulation (Berens et al., 2017), both of which represent adaptive responses. HPA axis activation is a mediating mechanism by which environmental factors influence well-being (Gunnar and Quevedo, 2007; Lupien et al., 2001). In humans, the hypothalamus acts in response to a stressor first, by releasing corticotropin releasing hormone. Cortisol, the end-product of this downstream process, works to break down fats, sugars, and proteins that the body can use as sources of energy when mobilizing toward the threat or stressor (Gunnar and Quevedo, 2007). The calibration of the HPA axis occurs through complex signaling pathways (Meaney, 2010) and the evolving development of the HPA axis is adaptive for those in high-stress conditions. There is also evidence that individual differences in HPA axis reactivity may be established in early development, as early as in-utero (Meaney, 2010).

HPA axis reactivity to stress, quantified as a blunted cortisol response, is observed in youth exposed to poverty and low income (Zalewski et al., 2012), as well as to adverse care in early life, including institutionalization and foster care (Koss et al., 2016). It has been hypothesized that early experiences of stress and adversity characterized by social stress and uncontrollability are particularly disruptive. Some evidence points to a larger effect size of ELS on cortisol reactivity among individuals who have experienced maltreatment (Bunea et al., 2017), providing support for a stress sensitization model of the HPA axis. Other research has demonstrated that blunted HPA axis reactivity persists into adulthood (Trickett et al., 2010), supporting the hypothesis that HPA axis reactivity may relate to trait-like symptoms, yet the current literature is largely limited by cross-sectional designs. Additionally, blunted HPA axis following chronic early life stress may also be maintained by recent stress, which is a confounding factor not always controlled for in studies examining the impact of ELS (Young et al., 2018).

3.2. Stress-induced elevations in inflammatory markers and contributions to anhedonia

While cortisol peaks in response to a threat or stressor and typically declines rapidly, inflammatory cytokines illustrate a more dynamic response in which cytokines remain elevated during recovery from stress (Slavich and Irwin, 2014). Pro-inflammatory cytokines are released during inflammation to heal damaged tissue from infections, promote neurogenesis and growth during different stages of development, and even trigger specific behavioral changes (Dantzer et al., 2008). Chronic activation of the immune system with repeated stressors tends to result in reduced reward responsiveness or reward seeking behavior (Dantzer, 2018). Key inflammatory cytokines, such as interleukin (IL-6) and tumor necrosis factor (TNF-α), alter neurotransmission and may contribute to the development of depression (Haroon et al., 2012). A meta-analysis found that exposure to childhood trauma is associated with heightened concentrations (i.e., 3 mg/L) of inflammatory cytokines IL-6, TNF-a, and C-reactive protein (CRP) in adulthood. Elevated TNF-a and IL-6 were associated with sexual abuse and physical abuse, while elevated CRP was associated with parental absence (Baumeister et al., 2016). A similar pattern is observed in rodent models of ELS, wherein repeated maternal stress in early life increases pro-inflammatory signaling (e.g., IL-6, TNF-α); yet this is dependent upon later-life stress (Dutcher et al., 2020). Moreover, composite scores of several inflammatory cytokines are shown to positively correlate with adverse childhood experiences. Similar effects are shown for recent life stressors (Hostinar et al., 2015).

Higher composite scores of peripheral inflammation are also associated with reduced functional connectivity between the ventromedial prefrontal cortex (vmPFC) and VS, which in turn is associated with decreased motivation and greater anhedonia severity in depressed samples (Felger et al., 2015; Haroon et al., 2016; Harrison et al., 2009; Yin et al., 2019). The same effect is seen in women with childhood trauma (Mehta et al., 2020). These results suggest that inflammation may play a critical role in disrupting communication between the vmPFC and VS to influence reward processing and mood. A question remains regarding the extent to which alterations in the stress response system persist over time to contribute to anhedonia.

4. Conclusions

Foundational work shows that stress response systems are uniquely impacted by stressors in early life, and emerging evidence shows that ELS affects the development of neural circuitry related to reward processing (Birn et al., 2017; Hollon et al., 2015; Ironside et al., 2018; Novick et al., 2018; Smith and Pollak, 2020; Stanton et al., 2018). Many of the observed neurobiological effects of ELS parallel features that have been established in major depression (Heim et al., 2004). Stressful life events are one of the strongest predictors of depression symptom onset (Hammen, 2016; Slavich and Irwin, 2014), and individuals exposed to ELS are 2–4 times more likely to meet diagnostic criteria for MDD (LeMoult et al., 2019; Li et al., 2016; Nelson et al., 2017; Sahle et al., 2021). Collectively, evidence points to an anhedonic phenotype resulting from ELS. Reward-related neural circuitry is vulnerable to the effects of chronic stressors in early life. Higher rates of MDD in ELS-exposed individuals may, at least in part, be explained by altered neural-immune interactions. Further exploration of these interactions in transdiagnostic anhedonic samples is necessary to support the putative impact of ELS on anhedonia beyond MDD more generally.

The sensitization model presented here is in accordance with theoretical perspectives that posit environmental influences on development are moderated by neurobiological susceptibility to the environment (Ellis et al., 2011; Gee and Casey, 2015). ELS-related inflammation effectively down-regulates reward-related brain circuitry and dampens reward sensitivity, thereby inducing anhedonia (Fig. 1) (Dantzer et al., 2008; Slavich and Irwin, 2014). Yet, mechanistic evidence for these

pathways remains to be elucidated. For example, HPA axis dysregulation may be a true, direct mechanism, or rather an indicator of other biological processes linking ELS and internalizing psychopathology (Koss and Gunnar, 2018). Some of the neurobiological changes reviewed here persist into adulthood; however, as highlighted here, some inconsistencies remain and replication is needed. Further, therapeutic studies have highlighted the resilience of neural and immune systems toward stressors. Targeted treatments to combat stress effectively reduce inflammation (Lindsay et al., 2022). Together, these findings support the conclusion that stressors rarely occur in isolation, and human studies that investigate early life stress should also assess recent life stress. It is critical to clarify the pathophysiological mechanisms by which stress confers risk for psychopathology to hasten the development of targeted interventions to prevent or reduce negative health outcomes of anhedonia (Simmons et al., 2020).

Limitations

The genetic or epigenetic contributions of early life stress, which are closely related to changes in HPA axis and neural and immune functioning, were beyond the scope of the current review. Additionally, there are additional neurotransmitter systems associated with reward processing, namely endogenous opioid (Oswald et al., 2021), that are implicated in early life stress and were not reviewed here. Finally, lifestyle factors that may account for the association between ELS and anhedonia or buffer against stressors (e.g., smoking, sedentary lifestyle, social support) were not reviewed here. Interested readers may refer to comprehensive reviews on these processes (Anacker et al., 2014; Bower et al., 2019; Gupta et al., 2024; Liu and Nusslock, 2018).

Future directions

Changes in HPA axis regulation, peripheral inflammation, and alterations in neural circuits subserving reward-processing have been identified as putative pathways between ELS and anhedonia (Felger et al., 2015; Hanson et al., 2018; Mehta et al., 2020; Miller et al., 2020; Stanton et al., 2018). Establishing the causality of stress on physiological changes and the role of stress in the etiology of anhedonia remains a challenge for the field. Anhedonia may arise in the absence of ELS, and recent stress remains an important confound. While inflammation has been implicated in ELS, it does not constitute the sole route by which ELS contributes to poor health outcomes, nor does ELS always result in changes in immune responses. Likewise, even though there are robust associations between adverse childhood experiences and mental and physical health outcomes, not everyone who experiences childhood adversity will experience poor outcomes. In resilient individuals, ELS does not lead to anhedonia or other psychological sequalae. ACE's have also been criticized for having "poor accuracy in predicting an individual's risk of later health problems" (Baldwin et al., 2021; Danese and Lewis, 2022). Several important areas for future study remain that may elucidate the pathway from ELS to anhedonia.

First, it is important to move beyond discussions of contributions of stress on anhedonia towards clarifying how stressors dysregulate neural functioning and how this dysregulation then reduces reward motivation. Future research towards this goal may provide mechanistic evidence for blunted neural reward functioning following ELS. Second, neural and immune systems do not operate independently, and interactions between these and psychological symptoms should be further explored. Future studies investigating the mechanisms reviewed here as mediators between ELS and anhedonia may take a multiple-mediation approach. Third, continued work is needed to understand factors related to ELS resilience. It is critical to evaluate the persistence of alterations in stress response, neural or otherwise, to characterize recovery from ELS. Future research would benefit from an exploration of individual differences in the potential pathways linking ELS and anhedonia. Fourth, sex differences in rates of MDD are consistently reported (Hammen, 2005; Hammen et al., 2009), and there is emerging evidence for differences in mesocorticolimbic neurobiology between males and females. Sex as a biological variable should be evaluated in future studies investigating ELS and anhedonia.

Fifth, regarding measures of chronic inflammation, recent work has highlighted novel markers that may aid in our understanding of stress-induced inflammation and contribute to effective therapeutics (Arbo et al., 2015; Rasmussen et al., 2020). One inflammatory marker is soluble urokinase plasminogen activator receptor (suPAR), which is less affected by acute stressors and represents global immune activity (Rasmussen et al., 2020). suPAR levels are elevated in individuals who have experienced adverse childhood events and recent life stressors (Bourassa et al., 2021). A second inflammatory marker is 18-kDa translocator protein (TSPO), which appears to play an important neuroprotective role and may be upregulated when the brain's resident innate immune cells, microglia, are activated in response to injury and inflammation (Hannestad et al., 2012; Sandiego et al., 2015). TSPO may also reflect microglial density, more specifically (Nutma et al., 2023). Increased TSPO expression in areas of the limbic system (e.g., hippocampus) is observed following chronic social defeat stress in mice (Nozaki et al., 2020). While these markers have been examined in depressed populations, to date, no study has examined suPAR or TSPO in transdiagnostic samples with anhedonia.

Lastly, while there is strong evidence that chronic stress disrupts neural and immune systems, it is not known whether therapies that "cultivate a healthy neuroimmune network", like those that promote positive psychological states, physical activity, and sleep, could reverse these impacts of stress (Bower et al., 2019). Therapeutic research is also needed to determine how changes such as these may moderate the proposed associations between ELS and anhedonia. Since stress exerts its greatest impact during sensitive periods of development, sensitive periods such as puberty and adolescence may represent windows of opportunity to intervene (Auerbach et al., 2014; Gupta et al., 2024). Most psychological and pharmacological treatments for MDD, and other conditions in which anhedonia is a prominent symptom, are not designed to target deficits in reward processing and positive emotion, with some exceptions (Craske et al., 2019). Future work should seek to identify "biologically defined subgroups with specific pathophysiologies and related symptoms" (Lucido et al., 2021) in order to develop targeted treatments that act on neural or immune targets. Improving our understanding of anhedonia using a multi-systems approach, following the many downstream effects of stress, may aid in the development of more specific and individualized treatments for anhedonia.

CRediT authorship contribution statement

Rachel Deanna Phillips: Writing – review & editing, Writing – original draft, Investigation, Conceptualization.

Declaration of competing interest

None.

Data availability

No data was used for the research described in the article.

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