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Brain mechanisms mediating effects of stress on reward sensitivity

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Acute and chronic stress have dissociable effects on reward sensitivity, and a better understanding of these effects promises to elucidate the pathophysiology of stress-related disorders, particularly depression. Recent preclinical and human findings suggest that stress particularly affects reward anticipation; chronic stress perturbates dopamine signaling in the medial prefrontal cortex and ventral striatum; and such effects are further moderated by early adversities. Additionally, a systems-level approach is uncovering the interplay among striatal, limbic and control networks giving rise to stress-related, blunted reward sensitivity. Together, this cross-species confluence has not only enriched our understanding of stress-reward links but also highlighted the role of neuropeptides and opioid receptors in such effects, and thereby identified novel targets for stress-related neuropsychiatric disorders.

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Introduction

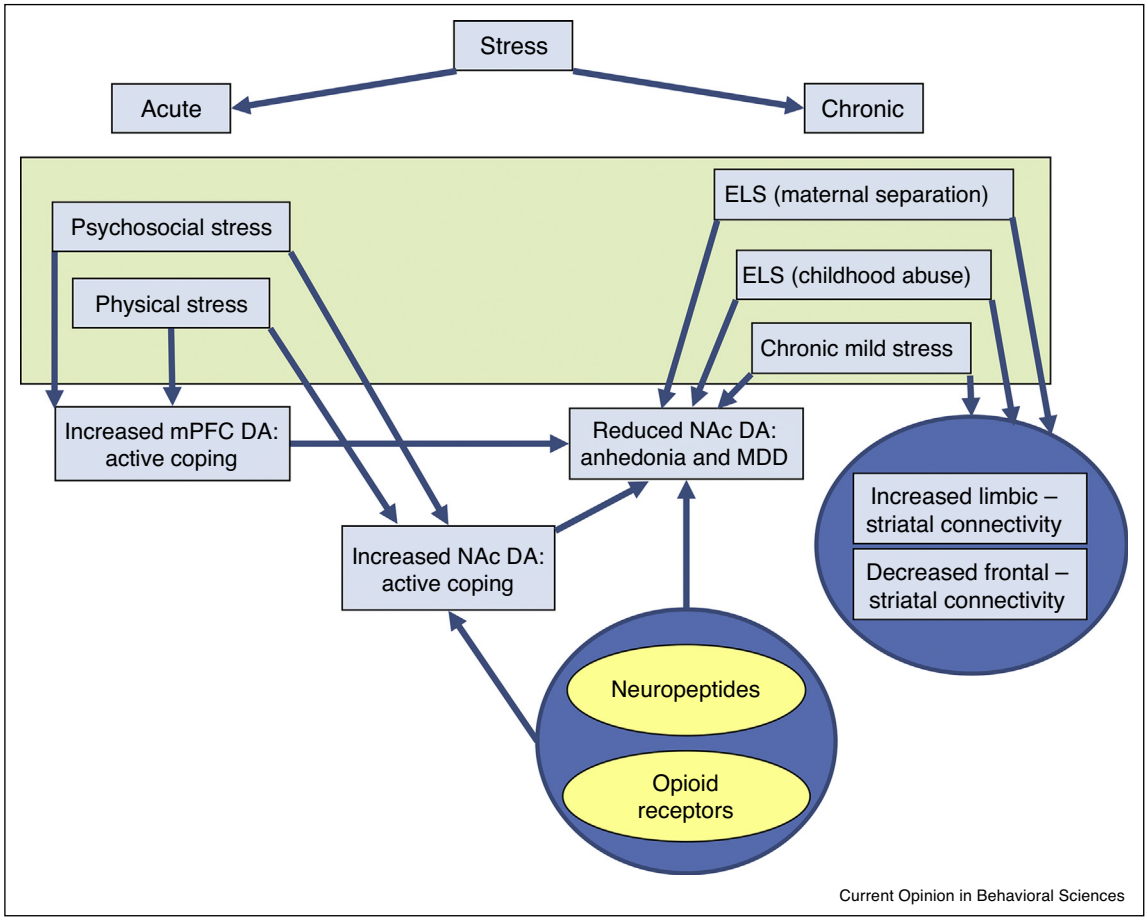
Stress exerts powerful effects on a myriad of cognitive (e.g., learning), affective (e.g., emotional responding), and motivational (e.g., willingness to pursue rewards) processes [1]. In the current review, we provide an update on the effects of stress on reward sensitivity, which has important implications for stress-related disorders, particularly major depressive disorder (MDD). The role of stress in the onset and maintenance of MDD is well established, with estimates suggesting that up to 80% of first Major Depressive Episodes (MDEs) are preceded by major life events [2,3]. In addition, chronic stressors are linked to more frequent relapse, treatment resistance, and higher depressive symptoms [3]. Critically, repeated uncontrollable stress has been linked to sensitization processes [3,4], whereby minor stressors are increasingly likely to trigger another MDE, particularly in individuals reporting early life stress (ELS) [5].

In parallel, preclinical models have shown that chronic stress induces anhedonic behaviors [6,7], highlighting anhedonia as a core feature of stress-induced MDD [8] — a hypothesis increasingly evaluated in humans [3]. However, the effects of acute and chronic stress are markedly different. Acutely, stress appears to increase reward sensitivity across species, with successful coping associated with recruitment of reward-related neural resources. When stressors become chronic and uncontrollable, downregulation in dopaminergic mesolimbic pathways and anhedonic behaviors emerge — changes that might contribute to stress sensitization. The overarching goal of this review is to synthesise recent literature on brain mechanisms mediating the effects of stress on reward sensitivity (Figure 1). Toward this end, we first examine the effects of both acute and chronic stress across species, and consider how ELS further shapes these effects. Next, we emphasize how a systems-level approach — extending inquiry from individual brain regions to neural networks — promises to better elucidate substrates implicated in stress-related effects on reward sensitivity and increase cross-species integration. We end by highlighting molecular targets that could be used to counteract the effects of stress on reward sensitivity and might represent promising treatment targets for stress-related neuropsychiatric disorders.

Neurobiological effects of stress on reward sensitivity

Preclinical and human studies have probed the effects of acute and chronic stressors on appetitive motivation. Behaviorally, acute stress is linked to an increase in incentive motivation and active coping, but severe, chronic stress abolishes these behaviors and leads to helplessness and anhedonic behaviors. These behavioral changes occur via dopaminergic modulation within mesocorticolimbic pathways. Specifically, acute stressors increase dopamine (DA) levels in the medial prefrontal cortex (mPFC) and ventral striatum (VS), particularly the nucleus accumbens (NAc), with mPFC effects observed earlier than the NAc [3]. However, uncontrollable chronic

Figure 1



Summary of main concepts discussed. Recent work across species has further elucidated (1) the effects of acute and chronic (including early life stress (ELS)) stress on dopamine (DA) function in the medial prefrontal cortex (mPFC) and striatal regions such as the nucleus accumbens (NAc); (2) connectivity between limbic, striatal and frontal regions; and (3) how these processes might be mediated by neuropeptides and opioid receptors.

stressors have differential effects on mesolimbic versus mesocortical DA systems. Thus, increased DA transmission in the NAc from an acute stressor becomes blunted with repeated stressors [9], reflected in a change in behavior from active coping to learned helplessness and reduced reward sensitivity. In contrast, mPFC DA signaling increases further and exposure to chronic stress amplifies responses of mesocortical DA neurons to a subsequent acute stressor [10]. Consistent with preclinical evidence, we recently showed that acute stress increased neural activation in the striatum (NAc, caudate) during reward anticipation in healthy controls [11]. Conversely, depressed individuals experiencing greater recent life stress recruited the mPFC more under stress when processing rewards [12•]. Because mPFC DA inhibits NAc DA, stress-induced mPFC responses and associated blunting of NAc DA might reflect increased vulnerability to MDD with chronic stress.

Relations between mPFC and NAc DA have been further explored using chronic mild stress (CMS) models, showing CMS-induced reductions in NAc DA [13] and reward motivation but increased DA receptor expression [14] in the mPFC. In addition, the effects of CMS on NAc DA activity were selectively augmented/blocked by mPFC activation/inactivation [15]. Stress-induced effects on NAc DA were reversed by the administration of the antidepressant escitalopram, but not in rats previously exposed to maternal separation [13]. Anhedonic-like behavior caused by CMS was also reversed by medial frontal bundle deep brain stimulation (DBS) [16]. However, DA depletion did not preclude DBS effects, suggesting that they were not dependent on DA. This indicates that, in addition to DA, other molecular mechanisms are implicated in stress-induced reward dysfunction (see section 'Novel molecular targets').

The role of early life stress

Several preclinical models (e.g., postnatal deprivation, maternal separation) have shown that exposure to early adversity leads to reduced motivation to pursue rewards in adult rats [3]. Similarly, maternal separation in marmoset monkeys elicited a reduction in reward motivation (but not consumption) [17]. These behavioral findings are complemented by reports that early adverse events have long-lasting effects on mesolimbic DA pathways [3]. Collectively, these preclinical data raise the possibility that humans exposed to ELS might be characterized by anhedonic phenotypes and abnormal reward-related mesocorticolimbic activations. Early [3] and more recent findings are consistent with this assumption. In a study of adolescent girls using a card number guessing task [18], number of years of household public assistance was positively associated with heightened response in the mPFC during reward anticipation. Another study incorporating this task [19] found that greater cumulative ELS predicted lower reward-related VS activity in adulthood. Furthermore, findings from 820 young adults [20] showed that those with relatively blunted reward-related VS reactivity and elevated ELS reported greater anhedonic symptoms. Similarly, lower striatal (pallidum) activation during reward anticipation was associated with greater depressive symptoms in maltreated youth [21]. Of note, among this abused sample, higher reward-related striatal activation predicted lower increases in depressive symptoms over time. Together with early reports that ELS was associated with reduced striatal activation during anticipation (but not consumption) of rewards [22,23], data across species converge in suggesting that reduced motivation and striatal activation to reward-predicting cues but potentiated mPFC activation are important sequalae of ELS. Conversely, preserved reward-related striatal activation might confer resilience against stress-induced disorders.

From regions to networks

Functional connectivity (FC) analyses of neuroimaging data can elucidate interactions between the mPFC and striatum in response to stress, and potential moderations from other networks [24]. In a human study employing a socially evaluated cold press stressor and self-control decision paradigm [25], stress increased the influence of rewarding taste attributes on choice and reduced self-control. Critically, stress increased task-dependent connectivity between mPFC, amygdala and VS, which correlated with cortisol levels. Moreover, increased stress levels were associated with decreased connectivity between mPFC and dorsolateral prefrontal cortex (dlPFC), a region activated when engaging self-control. These patterns suggest a role for decreased top-down control under stress resulting in an exaggerated (likely DA-mediated) mPFC response. Higher levels of anhedonia were associated with increased FC between NAc and mPFC in trauma-exposed individuals [26], highlighting possible downregulation of NAc by mPFC. Among 921 young adults (from the same sample as [20]), increased FC between the left VS and mPFC emerged in individuals with greater levels of ELS who also experienced greater levels of recent life stress, a pattern that was associated with depressive symptoms [27•]. This offers a potential network explanation for the previous findings of blunted VS reward reactivity in the same group, again, aligning with preclinical work. Trauma-exposed youth also exhibited [28] altered connectivity in the salience network (SN) and the association between trauma and a self-report measure of reward sensitivity was mediated by SN-insula connectivity.

Of note, similar findings have emerged in preclinical resting state fMRI. A recent study in rats revealed that ELS increased connectivity in the salience network and a number of pairwise interactions between the hippocampus and prelimbic, infralimbic cortex and NAc [29•]. Similarly, mice exhibited robust increases in FC after chronic stress within prefrontal, cingulate and striatal networks [30], with additional increases in between-network FC, including amygdala/prefrontal cortex and amygdala/cingulate cortex. Collectively, findings across species (Figure 2) highlight stress-induced increases in striatal connectivity with limbic regions and, conversely, decreases in striatal connectivity with regions associated with executive function. This suggests that bottom-up limbic responses to acute stress may, via striatal connections, override top-down cognitive processes resulting in preferential formation of habitual response systems (driven by limbic and reward regions), rather than those processes requiring cognitive control (driven by prefrontal regions) [31].

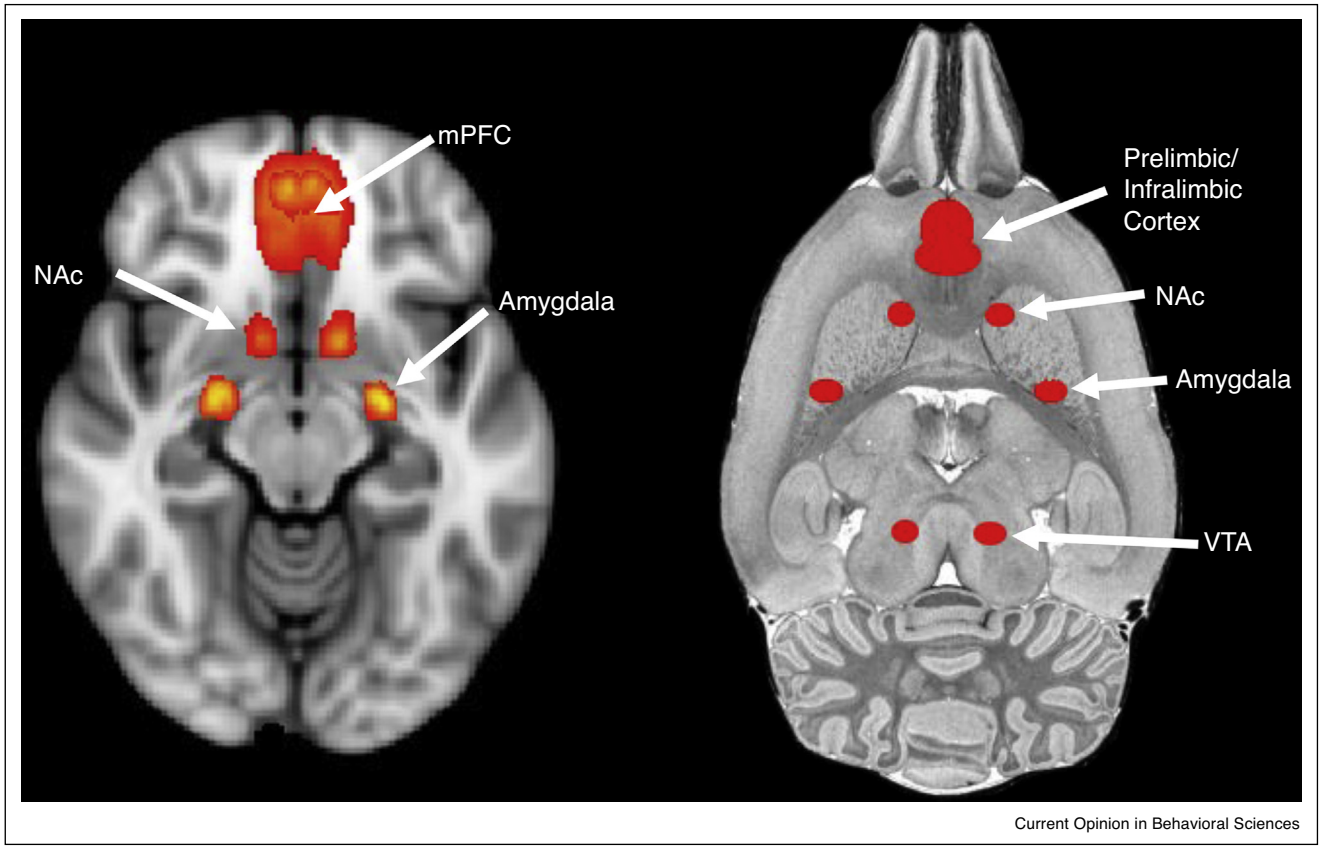
Novel molecular targets

Although corticotropin release factor (CRF) has been traditionally associated with behavioral and physiological responses to stress, recent data indicate that CRF release in the NAc plays a key role in potentiating motivation for cued rewards [32]. In line with this, a CRF1 antagonist blocked the enhancing effect of acute stress on reward motivation [33]. Moreover, chronic stress abolished CRF's ability to increase DA in the NAc up to 90 days after the stressor ended [34], and this effect was associated with a switch from appetitive to aversive motivation [34], which mirrors behaviors observed in MDD.

Due to their pivotal role in regulating stress and reward processing, opioid receptors (particularly, kappa opioid receptors (KOR) and mu opioid receptors (MOR)) as well as Nociceptin/Orphanin FQ (N/OFQ) receptors, have been strongly implicated in the emergence of stress-induced anhedonic behaviors.

With respect to KOR (Figure 3), studies have shown that acute stress elevates dynorphin in ventral tegmental area

Figure 2



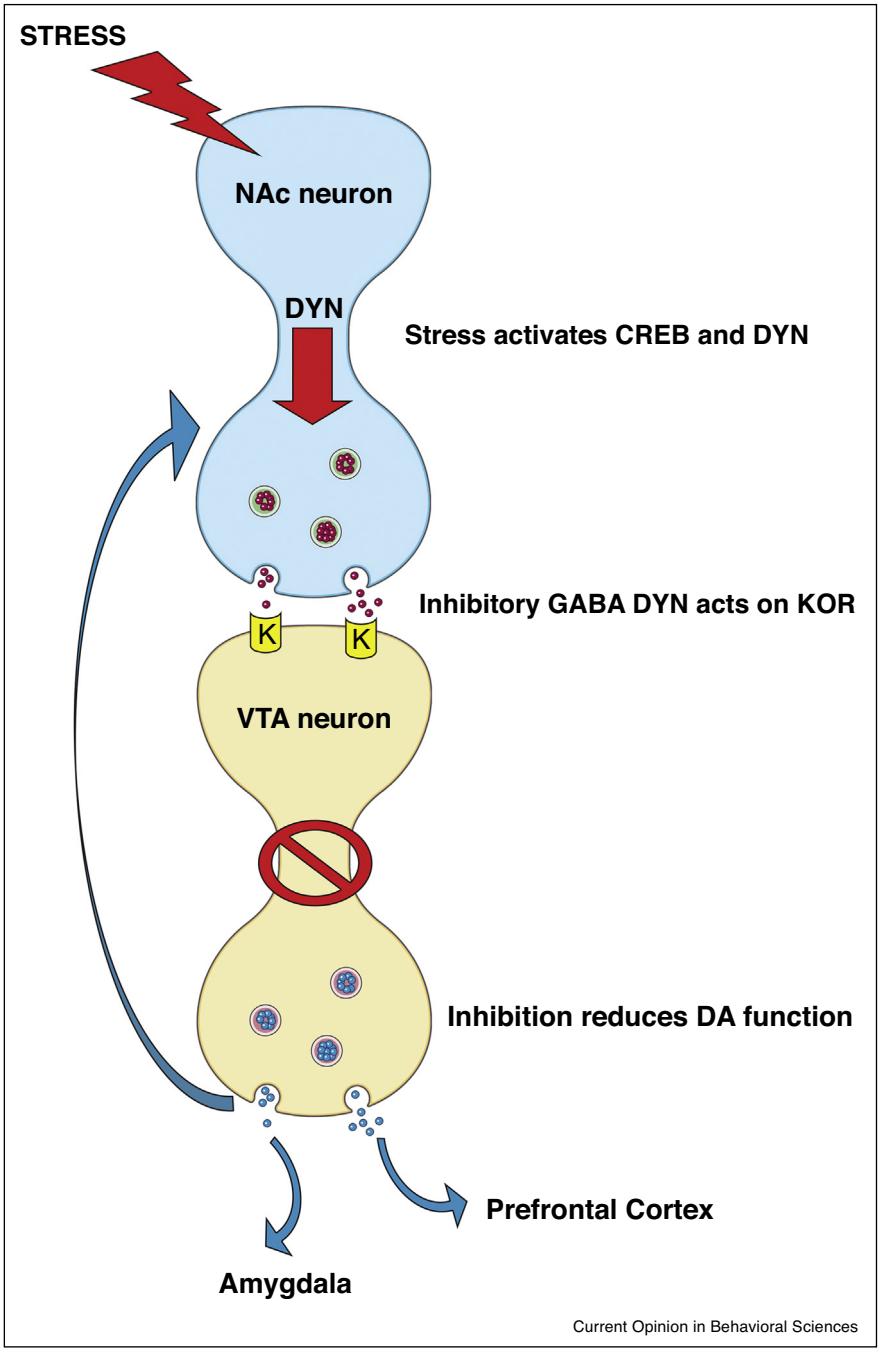
Limbic and reward regions in the human and rat brain. Human regions based on Harvard-Oxford Cortical and Subcortical atlas and overlaid on a canonical structural image (part of the FMRIB software library [48]). Rat regions based on atlas identified in [49] and overlaid on a structural Sprague Dawley rat brain [50]. *Abbreviations* — NAc: nucleus accumbens; mPFC: medial prefrontal cortex; VTA: ventral tegmental area.

(VTA) DA neurons, resulting in prolonged activation of KORs [35], which dampens DA function in the NAc and leads to anhedonic phenotypes [36••]. Interestingly, social isolation early in life has been shown to increase this KOR downregulation of NAc DA [37], indicating that ELS further potentiated these effects. In humans, a recent Positron Emission Tomography (PET) study indicated that KOR availability in an amygdala–anterior cingulate cortex–VS neural circuit was related to dysphoric (including anhedonic) symptoms following trauma [38], suggesting a KOR-based mechanism implicated in the effects of chronic stress on depressive symptoms.

Recent data highlight the role of MOR in modulating mesolimbic DA pathways as well as their stress-buffering effects. Specifically, mu-opioid-acting compounds have been found to activate mesolimbic DA pathways through the removal of inhibition from GABA interneurons, and these effects are dependent on MOR [39]. Following chronic corticosterone exposure (a manipulation that induces depressive behavior), administration of Tianeptine (a full MOR agonist [40]) reduced anhedonic behavior [41] but not in MOR-deficient mice. In a human study employing the Trier Social Stress Test, acute administration of the mu-opioid partial agonist Buprenorphine reduced cortisol response and threat perception [42]. The role of mu-opioids in modulating stress responses was further examined in a recent PET study using the selective MOR radioligand [^{11}C]Carfentanil and a psychosocial stressor [43•]. During social rejection, controls had increased activation in the NAc, bilateral amygdala, thalamus and periaqueductal gray area, while MDD individuals only had deactivation in the bilateral amygdala. This suggests that opioid response to acute stress in reward-related regions may be key to enabling the 'active coping' mechanism, which is absent in chronic stress and MDD.

More recently, the N/OFQ system has emerged as a promising mechanism underlying the emergence of stress-induced anhedonic behaviors. Several lines of evidence are consistent with this assumption [44,45]. First, stress and manipulations inducing depression-like behaviors have been found to upregulate N/OFQ receptors

Figure 3



Effects of stress on kappa opioid receptors and dopamine function. A working model of the effects of stress on kappa opioid receptors (KOR) and dopamine (DA): stress increases the transcriptional factor CREB (cAMP response element binding protein) in the nucleus accumbens (NAc), which potentiates the opioid peptide dynorphin in this region. Dynorphin acts on KORs, inhibiting DA release from the ventral tegmental area (VTA), which has downstream effects on NAc, prefrontal cortex and amygdala, and gives rise to depression and anxiety-related disorders, including blunted reward sensitivity.
Source: Figure adapted with permission from Ref. [36••].

(NOP). Second, NOP receptors are localized on dopaminergic nuclei (including the VTA) and NOP receptor agonism inhibits DA neurotransmission in the VTA and NAc. Third, NOP receptor antagonists have antidepressant-like effects in rodents and reverse stress-induced anhedonic behavior [46]. Fitting with this evidence, in a recent rat study, we found that a chronic stressor (social defeat) induced an anhedonic phenotype

and increased N/OFQ peptide mRNA levels in the striatum [47••]. Additionally, N/OFQ peptide and NOP receptor mRNA levels in key regions implicated in reward processing and stress regulation (VTA, striatum, cingulate) correlated with anhedonic deficits. These findings suggest that NOP receptor upregulation plays a critical role in the emergence of stress-related anhedonic phenotypes. Together, these data indicate that opioid neuropeptidergic systems may be promising targets in the development of new antidepressant and anxiolytic drugs, which is reflected in the number of current clinical trials in this area [36••].

Conclusions

Insights from preclinical work on DA function in response to both acute and chronic stress needs closer integration with human work. The increased availability of neuroimaging data from ELS groups allows further elucidation of the effects of chronic stress on reward sensitivity, aligning with preclinical findings. In parallel, increased use of a systems-level approach relying on functional connectivity analyses across species has uncovered stress-induced hyperconnectivity between striatal and limbic networks but hypoconnectivity between striatal and control (prefrontal) networks, which might give rise to maladaptive (habitual) responses and poor stress regulation, culminating in the emergence of blunted reward sensitivity and stress sensitization. Of particular relevance, opioid neuropeptidergic markers have emerged as key mediators of stress-induced changes in hedonic behaviors and this research promises to open avenues for much-needed novel treatment targets for stress-related neuropsychiatric disorders.

Conflicts of interest

Over the past 3 years, Dr. Pizzagalli has received consulting fees from Akili Interactive Labs, BlackThorn Therapeutics, Boehringer Ingelheim, Pfizer and Posit Science, for activities unrelated to the current research. MI, MSK and PK have no conflicts of interest.

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- •• of outstanding interest

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