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Stress effects on the neural substrates of motivated behavior

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Abstract

Exposure to stress has profound, but complex, actions on motivated behavior and decision-making. These effects are central to core symptoms of a number of psychiatric disorders that are precipitated or augmented by stress, such as depressive disorders and substance use disorders. Studying the neural substrates of stress's effects on motivation has revealed that stress affects multiple targets on circuits throughout the brain using diverse molecular signaling processes. Moreover, stress does not have unitary effects on motivated behavior, but differences in the intensity, duration, intermittency, controllability and nature of the stressor produce qualitatively and quantitatively different behavioral endpoints. Unsurprisingly, the results of neuroscientific investigations into stress and motivation often open more questions than they resolve. Here we discuss contemporary results pertaining to the neural mechanisms by which stress alters motivation, identify points of contention and highlight integrative areas for continuing research into these multifaceted complexities.

Stressors engage an array of neural and endocrine systems, causing the mobilization of physiological and psychological resources that allow an organism to respond to the present challenge to its homeostasis and overall well-being. Although the subjectively aversive qualities of stress are often emphasized, responses to acute stressors are generally adaptive, beneficial to the individual and potentially critical for survival. Moreover, stress itself is not universally aversive, as we even actively seek out stress under the right circumstances. Many individuals find the stimulation of thrill rides, scary movies and rough-and-tumble play to be invigorating. Notably, such stressors tend to be relatively mild and transient and typically do not entail a complete loss of control. It is now widely recognized that severe or chronic stress, particularly when coupled with a lack of predictability or perceived lack of control, can cause a variety of long-lasting physiological changes that wreak havoc on multiple organ systems as well as contributing to cognitive and affective deficits characteristic of many neuropsychiatric disorders. Although much research has focused on

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stress effects on hippocampal-dependent memory functions¹ and emotional processing related to fear and anxiety², reward processing and decision-making has become an important domain for stress-related research. Chronic stress induction procedures, including, but not limited to, chronic mild stress^{3,4} and chronic social defeat stress⁵⁻⁷, are commonly used as rodent models for the induction of depressive-like symptoms such as anhedonia, social withdrawal and behavioral despair, as indicated by decreases in sucrose preference and social interaction and increased immobility in forced swim or tail suspension assays, respectively. Aside from the inherent limitations and challenges of fully modeling in rodents any psychiatric disorders that themselves are heterogeneous and imprecisely defined in humans⁸⁻¹², these stress-induction procedures nevertheless robustly affect several forms of motivated behavior that are amenable to precise circuit manipulation with contemporary genetic techniques¹³⁻¹⁵.

In the current Review, we highlight recent studies examining how stress affects decision-making and general motivational processes, as understanding how stress leads to reprioritization in these basic behavioral domains is a prerequisite to gaining greater insight into the contributions of stress to various forms of psychopathology.

First, we focus on the contributions of dopamine-releasing neurons in the ventral tegmental area (VTA) as well as consequences immediately downstream in the nucleus accumbens (NAc). Mesolimbic dopamine is widely considered to be critical for learning the incentive value of stimuli or actions such that these learned values can be used by the organism to guide its future behavior¹⁶⁻²². This system thereby contributes to basic motivational processes through facilitating reward seeking, particularly that requiring animals to overcome behavioral challenges such as effortful response costs²³⁻²⁹. Moreover, mesolimbic dopamine also has been implicated in social aspects of motivated behavior³⁰⁻³³. Thus, much of our review focuses on studies investigating how a variety of stress-induction procedures influence multiple measures of motivated behavior through alterations in VTA dopamine neurons and the NAc. Recent work on this topic has not only described the nature of structural and physiological changes engendered by stress in this mesolimbic circuitry, but has also begun to reveal the specific neurotransmitter receptors, channels and intracellular signaling molecules underlying these stress-induced alterations.

Second, we discuss work investigating how stress affects decision-making by influencing which of multiple valuation systems organisms use to guide their selection of actions. Although this literature currently lacks the same level of molecular detail regarding the stress-induced systems-level alterations that have been identified in corticostriatal circuitry implicated in action selection, these investigations have spanned both human and nonhuman animal work and utilize sophisticated behavioral designs that are nonetheless amenable to more mechanistic future investigations. Across both sections we discuss current evidence pertaining to the complex interactions between multiple neural systems underlying motivated behavior and stress responsivity (Fig. 1), and we identify apparent inconsistencies in the literature and underexplored areas that are ripe for future investigations.

Stress effects on general motivational processes

The mesolimbic dopamine system has a central role in the control of motivated behavior. Recent studies examining different forms of motivated behavior following protracted stress manipulations have revealed that midbrain dopamine neurons have complex and perhaps contradictory roles in the behavioral consequences of different types of stressors^{34–36}. Recent work from Tye and colleagues demonstrates how chronic stress can alter behavior via modulation of mesolimbic dopamine system activity³⁴. Specifically, 8–12 weeks of chronic mild stress caused a reduction in sucrose preference during a two-bottle choice test and a reduction in time spent struggling during a tail suspension test, both of which were restored to the levels of non-stressed control mice by acute phasic (30 Hz) stimulation of dopamine neurons in the ventral tegmental area (VTA) every 5 s throughout periods of these behavioral assays³⁴. Likewise, inhibiting VTA dopamine neurons in stress-naïve control animals reduced sucrose preference and increased immobility. These causal manipulations are consistent with the observation that chronic mild stress causes a 50% reduction in spontaneously active VTA dopamine neurons, mediated by a pathway involving the basolateral amygdala and ventral pallidum³⁷. Collectively these findings support the notion that stress-induced reductions in mesolimbic dopamine activity disrupt these projections' normal contributions to motivation and appetitive behavior^{16,27,29}.

In contrast, a series of studies from Han and colleagues revealed a distinct and counterintuitive role for mesolimbic dopamine in mediating animals' susceptibility to the behavioral alterations resulting from social defeat stress. Following 10 d of repeated social defeat stress, a subset of mice exhibited avoidance in a social interaction assay and were designated as 'susceptible' to this defeat stress³⁸. These susceptible mice also demonstrated reduced sucrose preference compared with unsusceptible mice and non-stressed controls³⁸. Rather than showing reduced population activity, however, VTA dopamine neurons of susceptible mice actually exhibited an increased firing rate^{36,38,39}. In previously unsusceptible mice, phasic (20 Hz) stimulation of VTA neurons during a second social interaction test caused social avoidance and reduced subsequent sucrose preference³⁵. Likewise, in a 2-d defeat procedure that is subthreshold for inducing the susceptible phenotype, phasic stimulation of VTA dopamine neurons either during the defeat bouts or during the social interaction test caused social avoidance and reduced subsequent sucrose preference, and phasic stimulation during the latter time point caused a lasting increase in the intrinsic excitability of these neurons³⁵. Following the full 10-d defeat procedure, VTA dopamine neurons of both susceptible and unsusceptible mice exhibited increased excitatory hyperpolarization-activated cation channel current (I_h) relative to non-stressed control mice^{36,39}, consistent with the previous finding that the stress-related peptide corticotropin-releasing factor (CRF) increases VTA dopamine neuron firing rates by enhancing I_h current⁴⁰. However, unsusceptible mice also showed upregulation of several voltage-gated potassium channels in the VTA³⁸ and corresponding increases in potassium channel currents³⁶ that may promote resilience by normalizing the excitability of these dopamine neurons following repeated defeat stress. Indeed, viral overexpression of the inwardly rectifying potassium channel Kir2.1 in the VTA of susceptible mice reduced the firing rate

of VTA dopamine neurons and eliminated behavioral avoidance in a subsequent social interaction test³⁸, as did administration of an I_h inhibitor into the VTA³⁹.

Notably, although potentiating I_h currents pharmacologically might have been expected to exacerbate the behavioral alterations exhibited by susceptible mice, this manipulation actually reversed their social avoidance and increased sucrose preference³⁶. Similar restorative effects were observed following phasic stimulation of VTA dopamine neurons for 20-min periods administered outside of any task context for 5 d. Although stimulation of VTA dopamine neurons in this instance did promote subsequent social approach and appetitive behavior, overall this finding is consistent with the larger body of work suggesting that hyperexcitability of mesolimbic dopamine neurons contributes to social and motivational deficits following defeat stress. In particular, both the pharmacological and stimulation treatments seemed to engage mechanisms of homeostatic plasticity, increasing potassium channel currents and thereby reducing the firing rates of VTA dopamine neurons in these previously susceptible mice. Thus, this series of studies demonstrated remarkable internal consistency and mechanistic detail even though the notion that increased mesolimbic dopamine neuron activity promotes susceptibility to stress may be surprising.

These studies raise an apparent conundrum regarding the contributions of mesolimbic dopamine to stress-induced effects on motivated behavior. In the one common behavioral measure between these studies, both chronic mild stress and repeated social defeat stress (for a subset of animals) caused reductions in sucrose preference. But these distinct stressors caused opposing changes in VTA dopamine neuron activity, and causal manipulations of these neurons either alleviated or exacerbated the behavioral consequences of each stressor. On the one hand, chronic mild stress reduced the number of spontaneously active VTA dopamine neurons³⁷ and phasic stimulation during the two-bottle choice test restored sucrose preference to control levels³⁴. On the other hand, susceptibility to social defeat stress was associated with increased VTA dopamine neuron firing rates^{36,38,39} and phasic stimulation during subthreshold defeat or during the post-defeat interaction test in unsusceptible mice was sufficient to cause subsequent reductions in sucrose preference³⁵. These divergent contributions of dopamine to changes in sucrose preference following each type of stressor are particularly intriguing given that others have reported that congenitally dopamine-deficient animals retain the ability to form and express preferences for sucrose⁴¹ and pharmacological depletion or antagonism of mesolimbic dopamine does not alter sucrose preference following extensive training in stress-naïve animals⁴². Nevertheless, both series of stress studies^{34–36} provided causal evidence that acute manipulations of mesolimbic dopamine altered performance in this simple assay and mediated motivational changes following the different forms of stress.

Moreover, the physiological consequences of social defeat stress were specific to VTA neurons projecting to the NAc; indeed, VTA neurons projecting to the medial prefrontal cortex (mPFC) exhibited opposite physiological changes following social defeat stress^{35,36}. Although the projection targets of dopamine neurons affected by chronic mild stress have not been fully examined, pharmacological blockade of dopamine receptors in the NAc increased immobility in the tail suspension test and prevented any stimulation-induced increase in struggling³⁴, implicating mesolimbic dopamine, but leaving the question of

whether mesocortical dopamine has a role in the consequences of chronic mild stress open. Further direct comparison across studies is challenging given the numerous methodological differences—from the timing of dopamine neuron stimulation relative to the stress induction and behavioral tests to the pathway- and cell type-specificity of each study's approaches, and a variety of other subtle, but potentially important, differences (for an extensive discussion, see ref. 43)—but the severity and type of stressors may have contributed to these divergent findings. Indeed, Grace and colleagues have shown that, in addition to chronic mild stress reducing VTA dopamine neuron population activity³⁷, acute stressors such as restraint or repeated foot shock increased this population activity^{44,45}. These stressor-specific changes in population activity, tonic firing rate or excitability of VTA dopamine neurons in anesthetized animals or *ex vivo* slice preparations permit inferences and the generation of new hypotheses regarding the discrepant behavioral effects observed, but there is not always a straightforward relationship between these measures of basal activity and the effect of specific behavioral events on dopamine transmission. For example, although CRF in the VTA increased dopamine neuron firing rates⁴⁰, intra-VTA CRF attenuated the phasic dopamine response to reward delivery without affecting the response to presentation of reward-predictive cues in behaving animals⁴⁶. Indeed, CRF in the VTA differentially affected mesolimbic dopamine release evoked by stimulation of distinct inputs to the VTA. Thus, in conjunction with the growing emphasis on efferent projection-specific heterogeneity of midbrain DA neurons^{35,36,47–49}, further characterization of the specific roles of the many diverse inputs to dopamine neurons^{49–51} will be critical for gaining a more complete understanding of how different types of stressors affect this circuitry and influence motivated behavior.

In addition to the regulation of firing of midbrain dopamine neurons, stress also can alter mesolimbic dopamine transmission at the terminal level in the NAc. CRF receptors are found at dopamine neuron terminals in the NAc, and their activation by CRF augments evoked dopamine release in a concentration-dependent manner in stress-naïve animals⁵². Moreover, CRF infusion into the NAc of behaving animals induces a preference for the CRF-paired location⁵², enhances the ability of appetitive Pavlovian-conditioned stimuli to invigorate instrumental reward-seeking behavior⁵³ and accelerates social bond formation⁵⁴. Thus, this stress-related peptide acts in the NAc to positively mediate appetitive behavior in stress-naïve animals. However, after repeated forced swim stress, CRF in the NAc no longer increases dopamine release and now induces a conditioned place aversion rather than preference. This attenuation of CRF-potentiated dopamine release lasts at least 90 d after the stress induction and is mediated by glucocorticoid receptors, as CRF retains the ability to increase dopamine release when mice are pretreated with the glucocorticoid receptor antagonist RU486 before each swim stress session. Although the site of action and mechanism through which glucocorticoids regulate this CRF-dopamine interaction awaits further investigation, this work has begun to reveal a neural substrate through which repeated stress induces a switch in the affective significance of this stress-related signal's ability to regulate a critical modulator of motivated behavior. Other stress effects in the NAc include dendritic hypertrophy and increased spine density in medium spiny neurons (MSNs) following chronic mild stress as well as increased expression of several genes, including brain-derived neurotrophic factor (*Bdnf*)⁵⁵. Increased dendritic spine density⁵⁶ and BDNF

levels³⁸ have been observed in the NAc of susceptible mice following repeated social defeat, exemplifying a point of convergence between these stress induction procedures. Notably, increased BDNF levels were also found in postmortem NAc tissue from depressed human patients³⁸. CRF signaling in the NAc is necessary for this social defeat stress-induced BDNF increase in susceptible mice, as both social avoidance and the increase in BDNF were blocked by intra-NAc administration of the CRF receptor antagonist alpha-helical CRF⁵⁷.

Although the combination of intra-NAc CRF and phasic stimulation of VTA neurons was sufficient to increase NAc BDNF levels in stress-naïve mice, their social interaction behavior remained unaffected, indicating that increased BDNF alone is not sufficient to induce social avoidance in the absence of actual stress experience⁵⁷. Moreover, the source of the BDNF necessary for defeat stress-induced social avoidance seems to be the VTA rather than in the NAc itself, as *Bdnf* mRNA levels in the NAc were unchanged in susceptible mice relative to unsusceptible and control mice, and BDNF knockdown in the VTA, but not NAc, reduced social avoidance and increased sucrose preference following repeated defeat stress³⁸.

Although these studies reporting increased MSN spine density did not specify which subpopulations exhibited these stress-induced alterations, additional work has demonstrated distinct morphological and physiological consequences in different MSN populations containing predominantly D1 versus D2 dopamine receptors. Specifically, D1-MSNs of mice susceptible to social defeat stress exhibited increased intrinsic excitability and a decreased frequency of miniature excitatory postsynaptic currents (mEPSCs), whereas D2-MSNs from susceptible mice had unchanged intrinsic excitability and an increase in mEPSC frequency⁵⁸. In contrast, unsusceptible, but not susceptible, mice had increased unitary EPSC amplitude specifically onto mushroom spines of D1-MSNs and decreased EPSC amplitude onto mushroom spines of D2-MSNs⁵⁹. Accordingly, specific manipulation of each pathway can differentially exacerbate or alleviate stress-induced behavioral alterations^{58,60}. Adding even greater complexity to the roles of these circuits in general motivational processes, these pathway-specific manipulations resulted in dissociable effects on distinct behavioral measures. For example, high-frequency stimulation of D2-MSNs for several days before and immediately after subthreshold defeat stress increased subsequent social avoidance, but had no effect on sucrose preference⁵⁸. Likewise, overexpression of β -catenin in the NAc prevented social avoidance and reduced forced-swim immobility following repeated social defeat stress, with the pro-social effect of β -catenin being mediated specifically by D2-MSNs and not by D1-MSNs, but this manipulation again did not affect sucrose preference⁶⁰. In contrast, repeated (but not acute) high-frequency stimulation of D1-MSNs after repeated defeat stress increased subsequent social interaction time and sucrose preference in previously susceptible mice, and inhibition of D1-MSNs induced social avoidance and reduced sucrose preference in previously unsusceptible mice, whereas neither manipulation of D2-MSNs had any effect⁵⁸. Notably, D1-MSN stimulation also increased subsequent sucrose preference in stress-naïve mice.

Although the long-term physiological consequences of these circuit manipulations remain unknown, a recent study provided mechanistic insight into a feeding-related peptide whose activity at D1-MSNs in the NAc contributes to stress-induced reductions selectively in

sucrose preference without affecting escape-related behavior in tail suspension or forced swim tests⁶¹. Specifically, 8 d of restraint stress caused reductions in sucrose preference and increases in immobility along with changes in synaptic physiology at D1-MSNs, but not D2-MSNs, that included NMDA receptor-dependent long-term depression, reduced AMPA/NMDA ratios and endocytosis of GluA2-containing AMPA receptors. Activation of melanocortin 4 receptor (MC4R) in the NAc by 2–3-h incubation with the endogenous MC4R ligand α -melanocyte-stimulating hormone recapitulated these stress-induced physiological changes in D1-MSNs without affecting D2-MSNs. Knocking down MC4Rs or blocking AMPA receptor endocytosis in the NAc selectively prevented the stress-induced reduction in sucrose preference without affecting stress-induced increases in immobility during tail suspension or forced swim tests. Notably, this repeated restraint stress also caused a reduction in food consumption and consequent cessation of normal weight gain, which were also prevented by these manipulations of NAc MC4R signaling. Other feeding-related signaling molecules potentially interact with stress signals and may affect motivated behaviors beyond food intake and sucrose preference. For example, the orexigenic hormone ghrelin is increased following repeated social defeat stress^{62,63}, and not only does it mediate the stress-induced preference for high-fat food⁶³, but it also reduces forced-swim immobility⁶². Given the recent resurgence of studies characterizing the detailed circuitry involved in appetite regulation using precise molecular genetic techniques to dissect the multitude of excitatory, inhibitory, neuropeptidergic and other modulatory interactions between a variety of hypothalamic and other limbic and brainstem nuclei^{64–72}, further examination of the reciprocal interactions between stress and feeding-related circuits represents an important area for ongoing research⁷³.

Collectively, these studies demonstrate that stress effects on general motivational processes remain a complex topic, but they also point toward promising avenues for future research that will continue to provide mechanistic insight into the molecular substrates contributing to these processes. In particular, the studies focusing on mesolimbic dopamine discussed above have highlighted the importance of future investigations of different types of stressors in controlled studies using otherwise equivalent neural perturbations and behavioral measures. Although the conclusions regarding the role of dopamine in mediating stress effects on motivated behavior differed across these previous studies, the investigators in each study demonstrated internally consistent effects of dopamine manipulations across multiple assays of motivated behaviors affected by stress. In contrast with these relatively coherent behavioral clusters or syndromes affected by mesolimbic dopamine manipulations, the subsequent examinations of pathway-specific manipulations immediately downstream in the NAc have revealed dissociable effects on these same behavioral measures. To the extent that certain behavioral assays or stress-induction procedures may be more relevant to or valid for modeling neuropsychiatric disorders in nonhuman animals, the molecular detail provided by these studies may contribute to the development of improved treatments that more selectively target specific symptoms and, ideally, the underlying etiological mechanisms causing a particular individual's pathology. As these findings also highlight that motivated behavior is of course by no means a unitary process, there remains the critical challenge of refining the existing behavioral assays to better understand what specific

psychological processes underlie any particular behavioral measure and how they are affected by a given molecular or circuit-level manipulation.

A promising complementary way forward entails using these mechanistic approaches in conjunction with more sophisticated behavioral procedures examining more specific aspects of decision-making processes. There is a growing body of literature on stress effects on economic decision-making, much of which comes from a top-down perspective that has not yet been able to capitalize on the molecular studies of stress effects on general motivated behaviors as building blocks. This discontinuity provides a major research opportunity to consolidate and reconcile the literature on the specific molecular processes underlying general motivated behavior and the decision-making literature, the latter of which has a less detailed analysis of the neural substrates but more precision in the cognitive functions affected by stress. Nonetheless, there are a few examples of studies that have begun to transcend the levels of analysis from molecular biology to cognition. Following acute restraint stress, animals exhibit decremented responding for food rewards, a change in motivation that is mediated by the action of endogenous CRF in the VTA⁴⁶. This effect can be recapitulated by administration of exogenous CRF into the VTA, which decreases the amplitude of phasic dopamine release in the NAc in response to food delivery⁴⁶. Indeed, direct manipulations of dopamine transmission in the NAc, such as local application of dopamine receptor antagonists or dopamine neurotoxins, produce a similar reduction in responding for food rewards^{74,75}, even though dopamine depletion does not alter hedonic responses to reward delivery⁷⁶. This action is argued to be a selective effect on effort-based decision-making, as, when tested in concurrent decision-making tasks, these manipulations of NAc dopamine bias animals' preferences away from rewards that are available for a high response requirement toward otherwise less desirable rewards (smaller quantity or less palatable food) available for a minimal response requirement^{25–28}. Thus, these data collectively suggest that following acute restraint stress, CRF acts in the VTA to reduce the excitability of dopamine neurons to reward delivery, decreasing dopamine release in the NAc, which selectively alters decision-making policies so that animals prefer rewards that are available at lower response costs (Fig. 2), that is, they exhibit anergia²⁵. When animals were tested in an effort-based decision-making task following acute restraint stress, this prediction held true⁷⁷. Thus, these studies demonstrate transparency to how some of the molecular changes associated with stress effects on general motivation processes could have direct effect on decision-making.

Stress and multiple valuation processes

To this point, we have treated reward valuation as a solitary process to understand the effects of stress on motivation. However, it is commonly accepted that dual, or even multiple, sets of valuation processes exist, differing in their cognitive demands and the resultant flexibility of behaviors controlled by different underlying associative structures. One such example of dual valuation processes is identified in instrumental behavior based on the representation of current goal information as opposed to purely stimulus-elicited responses, designated as goal-directed versus habitual, respectively. Across a series of behavioral, pharmacological and neuroimaging studies using human participants subjected to an acute stressor that combined both physical and social aspects (the socially evaluated

cold pressor test), Schwabe, Wolf and colleagues repeatedly demonstrated that this acute stress biased participants toward habitual behavior rather than goal-directed instrumental behavior. These researchers used an instrumental conditioning task developed for use with humans undergoing functional magnetic resonance imaging⁷⁸ (fMRI) and adapted from similar behavioral tasks employed with rodents^{79,80}. Briefly, participants first learned to associate different actions with specific rein-forcer outcomes (for example, chocolate milk or orange juice) and then were given the opportunity to consume one reinforcer to satiety to selectively devalue that outcome. In a subsequent post-devaluation test session in which neither outcome was delivered, participants' choices revealed whether their behavior was under goal-directed or habitual control: a preference for the action associated with the non-devalued option was indicative of goal-directed behavior, whereas an equivalent preference for the actions associated with the devalued and non-devalued options was indicative of habitual behavior. Schwabe *et al.* demonstrated that, although non-stressed controls exhibited goal-directed behavior in this task, the acute physical and social stress manipulation biased participants toward habitual control, as their behavior was insensitive to this change in action-outcome value in the first block of trials in the post-devaluation test session^{81,82}. This stress-induced insensitivity to outcome-selective devaluation was observed whether the stress induction occurred before initial acquisition of the instrumental responses⁸¹ or just before the post-devaluation extinction test session⁸². The latter finding indicated that stress affected performance rather than solely disrupting acquisition of goal-directed behavior, although the bias toward habitual behavior was longer lasting when the stressor occurred before acquisition. Notably, when the acute stressor occurred before initial acquisition, significantly fewer stressed participants than non-stressed controls were able to report explicit knowledge of the action-outcome contingencies⁸¹, but this explicit task knowledge was unaffected when the stressor occurred after acquisition⁸².

Following the observation that stress-induced changes in cortisol levels significantly correlated with individuals' probability of choosing the devalued option⁸², the authors subsequently investigated the contribution of specific stress-related neuroendocrine systems to this bias toward habitual behavior^{83–85}. In addition to this association between glucocorticoids and stress-induced habitual behavior⁸², the noradrenergic system also has been implicated in this bias toward habitual behavior, as administration of the β -adrenergic receptor antagonist propranolol before the stress manipulation prevented the shift toward habitual behavior induced by acute stress⁸⁴. Moreover, exogenous activation of both systems concurrently was sufficient to bias participants' decisions toward habitual behavior in the absence of any overt stressor^{83,85}. Specifically, in a double-blind, placebo-controlled design, participants were administered either the synthetic glucocorticoid hydrocortisone, the anxiogenic α 2-adrenoceptor antagonist yohimbine, both hydrocortisone and yohimbine, or placebo only, each in the absence of any stress manipulation. The combined administration of hydrocortisone and yohimbine rendered participants' behavior habitual. However, neither hydrocortisone nor yohimbine treatment on its own caused any difference from the placebo controls, as these three groups' behavior each remained goal-directed. A previous fMRI study using this behavioral task highlighted the recruitment of orbitofrontal (OFC) and ventromedial prefrontal cortex in the goal-directed selection of non-devalued actions over devalued actions⁷⁸. Although neither hydrocortisone nor yohimbine alone

affected the activation observed in these ventral prefrontal regions, the combined treatment significantly disrupted this activity pattern⁸⁵. These neuroimaging findings were consistent with the requirement of concurrent activation of glucocorticoid and noradrenergic systems to disrupt goal-directed behavior and induce a shift toward less-flexible, habitual behavior that was insensitive to changes in outcome value.

These effects of acute stress and exogenous activation of stress-related neuroendocrine systems were partially replicated in a recent rodent study⁸⁶. Following either an acute 60-min restraint stress or combined treatment with corticosterone and yohimbine, rats remained sensitive to outcome-selective devaluation, indicating that these manipulations were not sufficient to render the animals' behavior habitual, in contrast with the previous human studies. However, a more severe stressor (a 60-min sequence of 20-min restraint, 20-min on an elevated platform and another 20-min restraint plus five tail shocks, all with loud music playing in a brightly lit novel room during the rats' dark cycle) did disrupt animals' sensitivity to devaluation. Although these findings in rats were only partially consistent with those from the human studies described above, it is noteworthy that these manipulations in rats were all conducted just before the post-devaluation choice tests, well after initial acquisition of the action-outcome contingencies. Although the stress manipulation in these human studies did bias participants toward habitual behavior regardless of whether the stress induction occurred before initial acquisition or only just before the post-devaluation test, the effects were stronger and longer lasting when the stress manipulation occurred before acquisition^{81,82}. Moreover, these studies collectively highlight that differences in stressor severity or other parameters potentially could account for the inconsistencies observed across studies. In the studies with human subjects, stress-induced increases in habitual behavior have consistently been observed when social and physical stressors were administered in combination, but how these stressors might affect behavior when given in isolation has not been tested. In the rodent study, only the combined stressor, but not the single restraint stress, significantly disrupted goal-directed behavior⁸⁶. Surprisingly, however, both stressor types caused comparable increases in the rats' plasma corticosterone levels, perhaps indicating that this physiological metric is not sufficiently sensitive to detect the differences in psychological severity between these two stress manipulations. Although further studies are required to more systematically investigate the effects of stressor type and severity on goal-directed versus habitual control of behavior, these studies collectively provide initial evidence for certain acute stressors biasing both humans and rodents toward habitual behavior.

Studies examining the effects of chronic stress on instrumental behavior have yielded more consistent results across species, indicating that chronic stress biases animals toward habitual behavior. In one study, rats were subjected to 21 d of chronic unpredictable stress that included randomly interleaved bouts of social defeat, forced swim and restraint stress⁸⁷. Following 12 d of instrumental training, chronically stressed rats' behavior became insensitive to reinforcer devaluation and changes in action-outcome contingencies, indicative of habitual behavior, whereas non-stressed control rats remained goal-directed. These stressed rats exhibited dendritic atrophy in the medial prefrontal cortex and dorsomedial striatum, coupled with hypertrophy in the dorsolateral striatum. Insensitivity to outcome devaluation and parallel corticostriatal alterations were also observed in human

participants following prolonged stress⁸⁸. This fMRI study examined instrumental behavior in medical students who had recently completed their medical residency selection exam (that is, after a long and stressful preparation period) versus a control group of medical students who had not recently prepared for this exam. Not only did chronic stress bias the former group toward habitual behavior, but it was also associated with changes in neural structure and function: morphological hypertrophy and increased activity were observed in the putamen, whereas atrophy and reduced activity were observed in the caudate of the stressed group relative to controls, and atrophy was also observed in the ventromedial prefrontal cortex of the stressed group. Another rodent study demonstrated that chronic delivery of corticosterone via drinking water recapitulated this bias toward habitual behavior, as corticosterone-treated animals became insensitive to both reinforcer devaluation and contingency degradation⁸⁹. This study also demonstrated that glucocorticoid receptors and prefrontal BDNF have dissociable roles in habit formation and general motivation, respectively. Thus, these experiments lay the foundation for future investigations of molecular mechanisms underlying stress-induced biases toward habitual behavior. Moreover, such investigations represent a promising avenue for integration with additional recent human studies suggesting that stress preferentially disrupts prefrontal-dependent cognitive computations contributing to goal-directed decision-making⁹⁰, as well as potentially aligning more broadly with the extensive body of cross-species work investigating the mechanisms through which stress alters prefrontal circuitry supporting working memory and other forms of cognitive flexibility^{91–94}.

Summary and conclusions

In this Review, we have not comprehensively cataloged the extensive literature on the effects of stress on motivation and decision-making, but instead highlighted contemporary areas of research and the key parameters that may affect their interpretation. As we have noted, the effects of stress on neural substrates related to motivated behavior are numerous and complex, and it is likely that the existing knowledge is just the tip of the iceberg. As such, the existing data at times seem to be confusing and even contradictory, no doubt because they are incomplete. We have emphasized that the different stress-induction protocols may have important bearing on the results, perhaps most importantly differences in the intensity, duration, intermittency and controllability of stressor exposure and differences between social and physical stress. Adding to the complexity is the concept of multiple valuation systems and the effects of stress thereon. Because stress biases the arbitration between these competing valuation systems, the cognitive substrates used by stress-naïve and stress-exposed individuals may be fundamentally different. In this regard, it is also noteworthy that other forms of behavioral and cognitive flexibility that are relevant to, but not directly subsumed in, motivation *per se* are also affected by stress, including those identified in spatial, working memory and set-shifting tasks^{91–99}. Despite these impediments, research into the neural substrates underlying stress effects on motivated behavior has been fruitful and continues to grow as a topic of research. It is clear that future studies will need to use different types of stressor exposure under otherwise identical conditions and to compare these effects using common metrics and analyses. Understanding this relationship better will no doubt prove to be increasingly complex, but it is a critically

important endeavor, as the link between stress and motivation is instrumental in the most prevalent psychiatric disorders, including substance use disorders and depressive disorders.

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Figure 1.

Key studies referenced in this review. Select works discussed in this review include stress effects on motivated behaviors mediated by dopamine neurons in the VTA^{34–37}, their downstream targets in the NAc^{55–61}, and interactions with neuropeptides such as CRF^{46,52,57} and BDNF^{7,38,57} in each region. The second section includes discussion of stress effects on different forms of instrumental behavior and corresponding structural and functional alterations in corticostriatal circuitry supporting these behaviors^{81–89}, including regions such as the mPFC, OFC, dorsomedial striatum (DMS) and dorsolateral striatum (DLS).

Figure 2.

Stress effects on effort-based decision-making. Acute restraint stress biases decision-making away from high-effort, high-reward options when a low-reward option is concurrently available for lower effort⁷⁷. The proposed mechanism for this effect is by reduction of reward-evoked dopamine release in the NAc as a result of release of CRF into the VTA during acute stress⁴⁶.