Published in final edited form as:
*Ann N Y Acad Sci*. 2008 October ; 1141: 105–130. doi:10.1196/annals.1441.030.

# Chronic Stress, Drug Use, and Vulnerability to Addiction

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## Abstract

Stress is a well-known risk factor in the development of addiction and in addiction relapse vulnerability. A series of population-based and epidemiological studies have identified specific stressors and individual-level variables that are predictive of substance use and abuse. Preclinical research also shows that stress exposure enhances drug self-administration and reinstates drug seeking in drug-experienced animals. The deleterious effects of early life stress, child maltreatment, and accumulated adversity on alterations in the corticotropin releasing factor and hypothalamic-pituitary-adrenal axis (CRF/HPA), the extrahypothalamic CRF, the autonomic arousal, and the central noradrenergic systems are also presented. The effects of these alterations on the corticostriatal-limbic motivational, learning, and adaptation systems that include mesolimbic dopamine, glutamate, and gamma-amino-butyric acid (GABA) pathways are discussed as the underlying pathophysiology associated with stress-related risk of addiction. The effects of regular and chronic drug use on alterations in these stress and motivational systems are also reviewed, with specific attention to the impact of these adaptations on stress regulation, impulse control, and perpetuation of compulsive drug seeking and relapse susceptibility. Finally, research gaps in furthering our understanding of the association between stress and addiction are presented, with the hope that addressing these unanswered questions will significantly influence new prevention and treatment strategies to address vulnerability to addiction.

### Keywords

chronic stress; early life stress; addiction risk; relapse; craving; mesolimbic dopamine

## Introduction

Stress has long been known to increase vulnerability to addiction. The last decade has led to a dramatic increase in understanding the underlying mechanisms for this association. Behavioral and neurobiological correlates are being identified, and some evidence of molecular and cellular changes associated with chronic stress and addiction has been identified. Human studies have benefited from the emergence of sophisticated brain-imaging tools and the cross examination of laboratory-induced methods of stress and craving and their association to specific brain regions associated with reward and addiction risk. This paper focuses primarily on the association between stress and addiction in humans but also draws from the broader animal literature to support the proposed hypotheses. A definition of stress and its neural underpinnings is presented with specific emphasis on its effects on motivation and behavior.



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Conflicts of Interest
The author declares no conflicts of interest.

In the context of strong epidemiological evidence linking early-childhood and adult adversity and risk of addiction, results from basic and human research that point to putative mechanisms underlying this association are presented. A critical role is seen for prefrontal circuits involved in adaptive learning and executive function, including controlling distress and desires/impulses, in the association between stress and addiction risk. However, several questions remain unanswered in understanding stress-related addiction risk, and these are reviewed in order to inform future research. Finally, the effects of chronic drug use on stress and reward pathways particularly with respect to relapse risk are examined. Future directions in addressing stress-related relapse risk in clinical settings are also discussed.

## Stress, Emotions, and Adaptive Behavior

The term "stress" refers to processes involving perception, appraisal, and response to harmful, threatening, or challenging events or stimuli.[1–3] Stress experiences can be emotionally or physiologically challenging and activate stress responses and adaptive processes to regain homeostasis.[2,4–6] Examples of emotional stressors include interpersonal conflict, loss of relationship, death of a close family member, and loss of a child. Common physiological stressors are hunger or food deprivation, sleep deprivation or insomnia, extreme hyper- or hypothermia, and drug withdrawal states. In addition, regular and binge use of many psychoactive drugs serve as pharmacological stressors. This kind of conceptualization allows the separate consideration of (1) internal and external events or stimuli that exert demands or load on the organism; (2) the neural processes that evaluate the demands and assess availability of adaptive resources to cope with the demands (appraisal); (3) the subjective, behavioral, and physiological activity that signal stress to the organism; (4) neuroadaptations in emotional and motivational brain systems associated with chronic stress; and (5) behavioral, cognitive, and physiological adaptation in response to stressors.

While stress is often associated with negative affect and distress, it can include "good stress" which is based on external and internal stimuli that are mild/moderately challenging but limited in duration and results in cognitive and behavioral responses that generate a sense of mastery and accomplishment, and can be perceived as pleasant and exciting.[1,3,6,7] Such situations rely on adequate motivational and executive functioning to achieve goal-directed outcomes and homeostasis.[3,6,8] However, the more prolonged, repeated, or chronic the stress—for example, states associated with increased intensity or persistence of distress—the greater the uncontrollability and unpredictability of the stressful situation, lower the sense of mastery or adaptability, and greater the magnitude of the stress response and risk for persistent homeostatic dysregulation.[1,6,9–11] Thus, the dimensions of intensity, controllability, predictability, mastery, and adaptability are important in understanding the role of stress in increasing risk of maladaptive behaviors such as addiction.

The perception and appraisal of stress relies on specific aspects of the presenting external or internal stimuli, personality traits, availability of internal resources (including physiological condition of the individual), prior emotional state (including beliefs and expectancies), and specific brain regions mediating the appraisal of stimuli as distressing, and the resulting physiological, behavioral, and emotional experiences and adaptive responses. Brain regions such as the amygdala, hippocampus, insula, and orbitofrontal, medial prefrontal, and cingulate cortices are involved in the perception and appraisal of emotional and stressful stimuli, and the brain stem (locus ceruleus and related arousal regions), hypothalamus, thalamus, striatal, and limbic regions are involved in physiological and emotional responses. Together these regions contribute to the experience of distress. Physiological responses are manifested through the two major stress pathways, namely corticotropin releasing factor (CRF) released from the paraventricular nucleus (PVN) of the hypothalamus, which stimulates adrenocorticotrophin hormone from the anterior pituitary, which subsequently stimulates the secretion of cortisol/

corticosterone from the adrenal glands, and the autonomic nervous system, which is coordinated via the sympathoadrenal medulary (SAM) systems.[4,12]

In addition, CRF has extensive influence in extrahypothalamic regions across the corticostriatal-limbic regions and plays a critical role in modulating subjective and behavioral stress responses.[13] Furthermore, central catecholamines, particularly noradrenaline and dopamine, are involved in modulating brain motivational pathways (including the ventral tegmental area or VTA, nucleus accumbens [NAc], and the medial prefrontal [mPFC] regions) that are important in regulating distress, exerting cognitive and behavioral control, and negotiating behavioral and cognitive responses critical for adaptation and homeostasis.[8,14,15] The hypothalamic and extrahypothalamic CRF pathways and central catechoamines target brain motivational pathways to critically affect adaptive and homeostatic processes. For example, different parts of the medial prefrontal cortex are involved in higher cognitive or executive control functions, such as controlling and inhibiting impulses, regulating distress, focusing and shifting attention, monitoring behavior, linking behaviors and consequences over time, considering alternatives before acting, and decision-making responses.[16,17] Psychosocial and behavioral scientists have elegantly shown that with increasing levels of emotional and physiological stress or negative affect, there is a decrease in behavioral control and increases in impulsivity, and with increasing levels of distress, and chronicity of stress, greater the risk of maladaptive behaviors.[18–27] Neurobiological evidence shows that with increasing levels of stress, there is a decrease in prefrontal functioning and increased limbic-striatal level responding, which perpetuates low behavioral and cognitive control.[28,29] Thus, the motivational brain pathways are key targets of brain stress chemicals and provide an important potential mechanism by which stress affects addiction vulnerability.

## Stress and the Development of Addictive Behaviors

There is a substantial literature on the significant association between acute and chronic stress and the motivation to abuse addictive substances (see[30] for review). Many of the major theories of addiction also identify an important role of stress in addiction processes. These range from psychological models of addiction that view drug use and abuse as a coping strategy to deal with stress, to reduce tension, to self medicate, and to decrease withdrawal-related distress,[31–37] to neurobiological models that propose incentive sensitization and stress allostasis concepts to explain how neuroadaptations in reward, learning, and stress pathways may enhance craving, loss of control, and compulsion, the key components in the transition from casual use of substances to the inability to stop chronic use despite adverse consequences, a key feature of addiction.[38–40] In this section, we review the converging lines of evidence that point to the critical role that stress plays in increasing addiction vulnerability.

### Chronic Adversity and Increased Vulnerability to Drug Use

There is considerable evidence from population-based and clinical studies supporting a positive association between psychosocial adversity, negative affect, and chronic distress and addiction vulnerability. The evidence in this area can be categorized into three broad types. The first includes prospective studies demonstrating that adolescents facing high recent negative life events show increased levels of drug use and abuse.[41–55] Negative life events such as loss of parent, parental divorce and conflict, low parental support, physical violence and abuse, emotional abuse and neglect, isolation and deviant affiliation, and single-parent family structure have all been associated with increased risk of substance abuse.

The second type of evidence is the association between trauma and maltreatment, negative affect, chronic distress, and risk of substance abuse. Overwhelming evidence exists for an increased association between childhood sexual and physical abuse and victimization and increased drug use and abuse.[56–60] There is also some evidence that recent negative life events

and physical and sexual abuse each exert somewhat independent risk on addiction vulnerability.[58] In addition to sexual and physical abuse, negative affect and chronic distress states are predictive of addiction vulnerability. Findings indicate that negative affect, including temperamental negative emotionality, is associated with substance abuse risk.[61–67] Several studies have also shown a significant association between prevalence of mood and anxiety disorders, including post-traumatic stress disorder (PTSD), behavioral conduct problems and increased risk of substance use disorders.[68–78] As stress is significantly associated with prevalence of mood and anxiety disorders and chronic psychiatric distress,[79,80] these associations raise the issue of whether psychiatric disorders conceptualized as chronic distress states may largely account for the significant association between stress and substance use disorders.

In the third type of evidence from population studies, recent research has examined lifetime exposure to stressors and the impact of cumulative adversity on addiction vulnerability after accounting for a number of control factors such as race/ethnicity, gender, socioeconomic status, prior drug abuse, prevalence of psychiatric disorders, family history of substance use, and behavioral and conduct problems.[81,82] Cumulative adversity or stress was assessed using a checklist method and by counting the number of different events that were experienced in a given period during the lifespan. The effects of distal (events occurring more than 1 year prior) and proximal stress experiences (events during the most recent 1-year period), and their effects on meeting criteria for substance use disorders were also assessed. The findings indicate that the cumulative number of stressful events was significantly predictive of alcohol and drug dependence in a dose-dependent manner, even after accounting for control factors. Both distal and proximal events significantly and independently affected addiction vulnerability. Furthermore, the dose-dependent effects of cumulative stressors on risk for addiction existed for both genders and for Caucasian, African-American, and Hispanic race/ethnic groups. The types of adverse events significantly associated with addiction vulnerability were parental divorce or conflict, abandonment, forced to live apart from parents, loss of child by death or removal, unfaithfulness of significant other, loss of home to natural disaster, death of a close one, emotional abuse or neglect, sexual abuse, rape, physical abuse by parent, caretaker, family member, spouse, or significant other, victim of gun shooting or other violent acts, and observing violent victimization. These represent highly stressful and emotionally distressing events, which are typically uncontrollable and unpredictable in nature. Table 1 summarizes the types of life events, chronic stressors, maltreatment, and individual level variables associated with addiction risk.

## Stress Exposure Increases Initiation and Escalation of Drug Self-Administration

There is some evidence from animal studies to support the notion that acute exposure to stress increases initiation and escalation of drug use and abuse (see[30,83] for reviews). For example, in animal models, social defeat stress, social isolation, tailpinch and foot-shock, restraint stress, and novelty stress are known to enhance acquisition of opiates, alcohol, and psychostimulant self-administration, with caveats relating to stressor type, genetic background of animals, and variations by drug type (see[84–87] for reviews). Also, although there are some negative findings, other evidence indicates that early life stress, using procedures such as neonatal isolation or maternal separation, and prolonged and repeated stressors representing chronic stress experiences, enhances self-administration of nicotine, psychostimulants, and alcohol and/or their acute behavioral effects.[88–93] Notably, sex plays an important role in stress-related sensitivity to the reinforcing effects of drugs and in stress enhancement of drug self-administration.[93–97] In humans, there is substantial evidence from prospective and longitudinal studies to support the effects of stress on drug use initiation and escalation in adolescents and young adults.[24,98–109] Furthermore, there are sex differences in the effects of early trauma and maltreatment on the increased risk of addiction.[74,110–114] Laboratory studies examining effects

of stress exposure on drug use are limited to legal drugs such as alcohol and nicotine, for ethical reasons. Nonetheless, there is evidence that stress increases drinking and nicotine smoking (see[83] for review), but the effects of drinking history, history of adversity, social stress, and expectancies are known to play a role in these experimental studies.

## Possible Mechanisms Underlying Stress Effects on Addiction Vulnerability

As evidence using diverse approaches has accumulated in support of a significant effect of stress on risk of addiction, this section examines research on neurobiological links between stress and reward pathways activated by abusive drugs. It is well known that the reinforcing properties of drugs of abuse involve their activation of the mesolimbic dopaminergic (DA) pathways, which include dopamine neurons originating in the ventral tegmental area and extending to the ventral striatum and the prefrontal cortex (PFC).[115–117] This pathway is also involved in assigning salience to stimuli, in reward processing, and in learning and adaptation.[14,118] Human brain imaging studies also support the role of these systems in drug reward, as psychostimulants, alcohol, opioids, and nicotine all activate the mesolimbic DA systems, in particular, the ventral and dorsal striatum, and such activity has been associated with the drug ratings of high or euphoria and craving.[119–126]

However, stress exposure and increased levels of glucocorticoids (GC) also enhance dopamine release in the NAc.[127–132] Suppression of GC by adrenalectomy reduces extracellular levels of dopamine under basal conditions and in responses to stress and psychostimulants.[131,133] However, chronic GC inhibits DA synthesis and turnover in the NAc,[134] suggesting that alterations in the hypothalamic-pituitary-adrenal (HPA) axis and glucocorticoids can significantly affect DA transmission. There is also evidence that, like drugs of abuse, stress and concomitant increases in CRF and glucocorticoids enhance glutamate activity in the VTA, which in turn enhances activity of dopaminergic neurons.[135–138] Human brain imaging studies have further shown that stress-related increases in cortisol are associated with dopamine accumulation in the ventral striatum,[125,139] and some evidence also reveals that amphetamine-induced increases in cortisol are associated with both dopamine binding in the ventral striatum and with ratings of amphetamine-induced euphoria.[140] Given that both stress and drugs of abuse activate the mesolimbic pathways, it is not surprising that each results in synaptic adaptations in VTA dopamine neurons and in morphological changes in the medial prefrontal cortex.[87,136,141,142]

In addition to a role in reward, a growing body of human imaging studies and preclinical data indicate that the ventral striatum is also involved in aversive conditioning, in experience of aversive, pain stimuli, and in anticipation of aversive stimuli.[143–146] Such evidence points to a role for the mesolimbic dopamine pathways beyond reward processing, and one that more broadly involves motivation and attention to behavioral response during salient (aversive or appetitive) events.[147–150] Furthermore, additional regions connected to the mesolimbic DA pathways and involved in reward, learning, and adaptive and goal-directed behaviors are the amygdala, hippocampus, insula, and related corticolimbic regions.[118,151] These regions, along with the mesolimbic DA pathways, play an important role in interoception, emotions and stress processing, impulse control and decision making, and in the addictive properties of drugs of abuse.[29,152]

## Stress Mechanisms Involved in Acquisition of Drug Self-Administration

Research has also examined whether stress-related increases in acquisition of drug self-administration are mediated by corticosterone (cortisol in humans). Findings indicate that HPA-activated corticosterone release is important for acquisition of drug self-administration.[131,153–155] Corticosterone administration also facilitates psychomotor stimulant effects of cocaine and morphine.[156] Furthermore, GC receptor antagonists injected into the VTA

decrease morphine-induced locomotor activity,[157] suggesting that activity of GC receptors in the VTA could mediate dopamine-dependent behavioral effects. Mice with deletion of the GR gene show a dose-dependent decrease in motivation to self-administer cocaine.[158] These data suggest that HPA-related corticosterone release could at least partially mediate the dopamine increases seen after drug administration.

Although in nonhuman primates the link between cortisol, dopamine, and drug self-administration has not been reported, there is evidence that stress related to social subordination is associated with lower levels of D2 receptors and higher cocaine self-administration.[159] In humans, positive emission tomography (PET) studies using [$^{11}$C]raclopride indicate that acute stress exposure increases dopamine release in the ventral striatum (VS). For example, in a small-sample study, Pruessner and colleagues (2004)[139] found that healthy individuals with low early-life maternal care showed greater dopamine release in the ventral striatum during an acute psychological stress task as compared to those with a history of high early-life maternal care. Furthermore, cortisol response during the stress task was correlated significantly ($r$ = . 78) to VS dopamine release. Oswald and colleagues (2005)[125] also demonstrated that acute amphetamine challenge-related subjective “high” responses and concomitant increase in dopamine in the VS were each significantly associated with amphetamine-induced cortisol responses. More recently, the same group has also shown a similar significant relationship between cortisol levels and dopamine release in the VS using a psychological stress task.[140] Although these data support the link between stress/cortisol and dopamine transmission, human research linking stress-induced changes in VS activity or dopamine binding and risk of addictive behavior is needed to directly establish the association between stress, mesolimbic dopamine, and addiction risk.

## Early Life and Chronic Stress, Dopamine Systems, and Drug Self-Administration

There is growing evidence from basic science studies that early-life stress and chronic stress significantly affect the mesolimbic dopamine pathways and play a role in drug self-administration. Repeated and prolonged exposure to maternal separation (MS) in neonatal rats significantly alters the development of central CRF pathways.[11] These animals as adults show exaggerated HPA and behavioral responses to stress.[160,161] Such physiological and behavioral changes are associated with altered CRF mRNA expression in the PVN, increased CRF-like immunoreactivity in the locus ceruleus (LC), and increased CRF receptor levels in the LC and raphe nuclei.[11] The adult animals also show decreased negative feedback sensitivity to glucocorticoids,[162] and these changes are accompanied by decreased GC receptor expression in the hippocampus and frontal cortex.[11,163] Decreased GABA receptor levels in noradrenergic cell body regions in the LC and decreased central benzodiazepine (CBZ) receptor levels in the LC and the amygdala have also been reported.[164] More importantly, MS rats show significantly elevated DA responses to acute stress along with increased stress-induced behavioral sensitization and robust behavioral sensitization to psychostimulant administration.[11,143,165] This cross-sensitization of stress and drugs of abuse is associated with enhanced release of DA in the NAc, lower NAc-core, and striatal DA transporter sites, and reduced D3 receptor binding sites and mRNA levels in the NAc shell.[166–168] In addition, chronic norepinephrine deficiency induces changes similar to sensitization that could be related to alterations in DA-signaling pathways.[169,170]

Early-life stress and prolonged and repeated stress also adversely affect development of the prefrontal cortex, a region that is highly dependent on environmental experiences for maturation.[171] The PFC, and particularly the right PFC, plays an important role both in activating the HPA axis and autonomic responses to stress and in regulating these responses.[171] For example, lesions of the ventromedial PFC result in enhanced HPA and autonomic responses to stress. High levels of glucocorticoid receptors are also found in the PFC, and

chronic GC treatment results in a dramatic dendritic reorganization of PFC neurons similar to that seen in the hippocampus.[172,173] Furthermore, early postnatal MS and social isolation result in abnormally high synaptic densities in the PFC and altered densities of DA and serotonin (5-HT) terminals throughout the medial PFC.[174] Social defeat stress also alters feedback from the PFC and contributes to drug self-administration.[84] Human studies on the neurobiological effects of child maltreatment document neuroendocrine changes as well as alterations in size and volume of prefrontal, thalamic, and cerebellar regions associated with maltreatment and with initiation of addiction.[175,176] Together, the data presented in this section highlight the significance of stress effects on mesolimbic and prefrontal regions involved in stress related behavioral control.

## Stress, Self-Control, and Addiction Vulnerability

High emotional stress is associated with loss of control over impulses and an inability to inhibit inappropriate behaviors and to delay gratification.[20,177,178] Neurobiological data indicate that stress impairs catecholamine modulation of prefrontal circuits, which in turn impairs executive functions like working memory and self-control.[17,28,179] There is also growing evidence that adolescents at risk for substance abuse who have experienced several of the stressors listed in Table 1 are more likely to show decreased emotional and behavioral control, and decreased self-control is associated with risk of substance abuse and other maladaptive behaviors.[104,152,180,181] Adolescents at risk for substance abuse are known to have decreased executive functioning, low behavioral and emotional control, poor decision making, and greater levels of deviant behavior and impulsivity.[24,152,182–184] The corticostriatal-limbic dopamine pathways have been associated with impulsivity, decision making, and addiction risk,[185,186] and as discussed in previous sections, specific regions of this pathway, such as the VTA, NAc, PFC, and amygdala, are highly susceptible to stress-related signaling and plasticity associated with early-life stress and chronic stress experiences. In a recent PET imaging study, Oswald (2007)[187] examined the effects of chronic stress and impulsivity on amphetamine-induced striatal dopamine release. These findings indicated that high trait impulsivity was associated with blunted right VS dopamine release. However, these effects were modified by a significant interaction with chronic life events stress. With low to moderate stress, dopamine release was greater in low than in high impulsive subjects, but with high stress, both groups showed low DA release. These findings demonstrate the important effects of stress and impulsivity on mesolimbic dopamine transmission and highlight the fact that both factors need to be carefully considered to fully understand the role of stress and impulsivity on addiction risk.

## Schematic Model of Stress Effects on Addiction

Figure 1 presents a schematic model of stress effects on addiction. It highlights cross-sensitization of stress and drug abuse on specific behavioral and neurochemical responses and indicates the common neurobiological pathways upon which both stress and drugs of abuse act. Column A lists three types of vulnerability factors: (1) developmental/individual-level factors such as frontal executive function development, negative emotionality, behavioral/self-control, impulsivity, or risk taking, and altered initial sensitivity to rewarding effects of drugs; (2) stress-related vulnerability factors such as early adverse life events, trauma and child maltreatment experiences, prolonged and chronic stress experiences; and (3) genetic influences and family history of psychopathology and addiction, which have not been discussed here but have significant interactive effects on addiction risk and in emotion and stress markers.[188–194] Each of these factors may influence each other to significantly affect alterations in neurobiological pathways involved in stress regulation and cognitive and behavioral control (column B). Specific synaptic changes in these pathways at molecular and cellular levels[118,195] provide the basis for the mechanism by which stress and individual and genetic factors in column A interact to increase risk of maladaptive behaviors represented in column C. The model suggests that stress experiences in the presence of these vulnerability factors result in

maladaptive stress and self-control responses that increase addiction risk. The specific mechanism by which the maladaptive stress responding increases this risk involves dysregulation in brain stress circuits, particularly the CRF and NE systems, and their interactions with the mesocorticolimbicstriatal dopamine pathways and its modulation by glutamate and GABA.[114,196,197] Furthermore, recent evidence suggests that stress regulatory molecules, including neuropeptides such as neuropeptide (NPY) endocannabinoids, and neuroactive steroids play a role in addiction vulnerability.[198–203]

## Drug Use and Abuse and Changes in Stress and Reward Pathways

### Acute and Chronic Drug Use and Changes in Stress Responses

Acute administration of the most commonly abused drugs such as alcohol, nicotine, cocaine, amphetamines, and marijuana that activate brain reward pathways (mesocorticolimbic dopaminergic systems) also activate brain stress pathways (CRF-HPA axis and the autonomic nervous system pathways) with increases in plasma adrenocorticotropic hormone (ACTH) and corticosterone, changes in heart rate and blood pressure, and skin conductance responses.[204–217] On the other hand, acute exposure to opiates decreases cortisol levels in humans.[218,219] Regular and chronic use of these drugs is also associated with adaptations in these systems that are specific by drug. For example, changes in heart rate and heart rate variability (HRV) are reported with regular and chronic alcohol use.[220–222] Sustained increases in HPA axis function in the case of psychostimulants, and tolerance to the inactivating effects of the drug in the case of morphine, nicotine, and alcohol has also been reported.[223–226] These direct effects of drugs of abuse on major components of the physiological stress response support their classification as pharmacological stressors.

Acute withdrawal states are associated with increases in CRF levels in CSF, plasma ACTH, cortisol, norepinephrine (NE), and epinephrine (EPI) levels.[38,211,216,227–231] Early abstinence is associated with high basal cortisol responses and a blunted or suppressed ACTH and cortisol response to pharmacological and psychological challenges in alcoholics and chronic smokers, while hyper-responsivity of HPA hormones in response to metyrapone has been reported in opiate and cocaine addicts.[232–236] Furthermore, withdrawal and abstinence from chronic alcohol is also associated with altered sympathetic and parasympathetic responses,[234,237–239] and altered noradrenergic responses to yohimbine challenge in early abstinence from cocaine has also been observed.[240] All of the above changes highlight the significant effects of drug use and abuse on physiological stress responses.

Although acute administration of drugs increases mesolimbic dopamine,[241] regular and chronic use of abusive drugs and acute withdrawal states down regulate mesolimbic dopamine pathways with decreases in basal and stimulated dopamine reported in several preclinical studies.[242–251] Chronic use of cocaine has also been shown to dramatically alter central noradrenergic pathways in the ventral and dorsal striatum, other areas of the fore-brain, and the ventromedial prefrontal cortex.[252,253] Human brain imaging studies corroborate these preclinical data, with reduced D2 receptors and dopamine transmission in the frontal and ventral striatum regions in alcoholics and cocaine abusers during acute withdrawal and protracted withdrawal (up to 3−4 months).[254–256] Furthermore, blunted dopamine release in the ventral striatum and anterior caudate was associated with a preference to self-administer cocaine over receiving money in human cocaine abusers.[257] These changes are similar to the effects of prolonged and repeated stressors on mesolimbic dopamine and norepinephrine deficiency noted in the previous section[134,187,258] and raise the question whether chronic drug effects on extrahypothalamic CRF, noradrenergic, or glucocorticoid systems may at least partially modulate these dopamine-related changes in the corticostriatal limbic dopamine pathways.

On the other hand, acute, regular, and chronic exposure to drugs results in "sensitization" or enhanced behavioral and neurochemical response to drugs and to stress. Synaptic alterations in the VTA, NAc, and medial PFC modulated by glutamate effects on dopamine neurons and CRF and noradrenergic effects on DA and non-DA pathways contribute to behavioral sensitization of stress and drugs of abuse.[210,259–262] In addition, increased levels of brain derived neurotrophic factor (BDNF) in the mesolimbic dopamine regions has been associated with increases in drug seeking during abstinence from chronic drug use.[263,264] Furthermore, behavioral sensitization observed with drugs of abuse and with stress are associated with synaptic changes in mesolimbic dopamine regions, particularly the VTA, NAc, and amygdala, and such changes contribute to compulsive drug seeking.[118,265] Thus, there are significant physiological, neurochemical, and behavioral alterations in stress and dopaminergic pathways associated with chronic drug use, which in turn could affect craving and compulsive seeking, maintenance of drug use, and relapse risk. It is not entirely clear how long these changes persist or the extent to which there is recovery or normalization of these pathways and responses in related functional responses.

## Altered Stress Responses and Craving with Chronic Drug Abuse

Clinical symptoms of irritability, anxiety, emotional distress, sleep problems, dysphoria, aggressive behaviors, and drug craving are common during early abstinence from alcohol, cocaine, opiates, nicotine, and marijuana.[30,266–269] A mild "negative affect" and craving state ensues postwithdrawal, associated with alterations in the stress and dopamine pathways.[37,197,250,270] The severity of the these symptoms has been associated with treatment outcomes, with greater dependence and abstinence severity predictive of worse treatment outcomes.[271–274] Drug craving or "wanting" for drug is conceptually different from other anxiety and negative affect symptoms as it comes from "desire" or a wish for a hedonic stimulus. However, with chronic drug use, the term becomes associated with a physiological need, hunger, and strong intent to seek out the desired object, thereby representative of the more compulsive aspects of craving and drug seeking identified by addicted patients.[274–277] In particular, craving and compulsive seeking is strongly manifested in the context of stress exposure, drug-related cues, and drug itself and can become a potent trigger for relapse.[30,274,278–281] Several recent models of addiction have presented the concept that this heightened craving or wanting of drug is the behavioral manifestation of molecular and cellular changes in the stress and dopamine pathways discussed in the previous section. Indeed some support for this idea comes from laboratory and imaging studies summarized below.

In my laboratory, we have examined the effects of stress and drug-related cues on drug craving in alcoholics, cocaine-dependent individuals, and naltrexone-treated, opiate-dependent individuals in recovery. Drug craving and stress responses were assessed in treatment-engaged, abstinent, addicted individuals who were exposed to stressful and nonstressful drug-cue situations and neutral relaxing situations, using personalized guided imagery procedures as the induction method.[282] Our initial findings indicated that in addicted individuals, stress imagery elicited multiple emotions of fear, sadness, and anger as compared to the stress of public speaking, which elicited increases in fear but no anger or sadness. In addition, imagery of personal stressors produced significant increases in cocaine craving, while public speaking did not.[283–285] Significant increases in heart rate, salivary cortisol, drug craving, and subjective anxiety were also observed with imagery exposure to stress and nonstress drug cues as compared to neutral relaxing cues in cocaine-dependent individuals.[285] More recently, we have shown that stress and alcohol/drug-related stimuli similarly increase craving, anxiety, negative emotions, and physiological responses in abstinent alcoholics and in naltrexone-treated, opiate-addicted individuals.[286,287] On the other hand, recently abstinent alcoholics and smokers show altered basal HPA responses and a suppressed HPA response as measured by cortisol to stress compared to their nonaddicted counterparts.[288–290]

In a more comprehensive assessment of the biological stress response in recently abstinent cocaine-addicted individuals, we reported that brief exposure to stress and to drug cues as compared to neutral relaxing cues activated the HPA axis (with increases in ACTH, cortisol, and prolactin levels) as well as the sympthoadrenomedullary systems, as measured by plasma norepinephrine and epinephrine levels.[282] Furthermore, we found little evidence of recovery or return to baseline in ACTH, NE, and EPI levels even more than 1 h after the 5-min imagery exposure. These findings were extended to directly compare abstinent cocaine-dependent individuals to a demographically matched group of healthy social drinkers, using individually calibrated personally emotional stress and drug/alcohol cue-related imagery compared to neutral imagery. Findings indicated that cocaine patients showed an enhanced sensitivity to emotional distress and physiological arousal and higher levels of drug craving to both stress and drug-cue exposure compared to controls.[291] Similarly, we also compared 4-week abstinent alcoholics to matched social drinkers. The recovering alcoholics at 4 weeks abstinence showed greater levels of basal heart rate and salivary cortisol levels compared to control drinkers. Upon stress and alcohol-cue exposure, they showed persistently greater subjective distress, alcohol craving, and blood pressure responses, but a suppressed heart rate and cortisol response compared to controls.[239] Interestingly, both cocaine patients and alcoholics show increased anxiety and negative emotions during drug-cue exposure, while social drinkers report lower levels of negative affect and anxiety with alcohol-cue exposure. These data provide direct evidence of high drug craving and altered hedonic responses to both stress and drug cues in addicted individuals compared to social drinkers (see Fig. 2). They also indicate that alterations in physiological stress responses are associated with high levels of stress-induced and cue-induced craving and distress states. The nature of the alterations are marked by increased emotional distress, heightened craving, altered basal responses, and blunted or suppressed physiological responses in abstinent addicted individuals compared to social drinkers.

Many studies have also examined brain regions associated with craving in addicted individuals. Exposure to drug cues known to increase craving increases activity in the amygdala and regions of the frontal cortex,[292–294] with gender differences in amygdala activity and frontal cortex response in cocaine-dependent individuals.[295,296] Cue-induced craving for nicotine, methamphetamine, or opiates also activates regions of the prefrontal cortex, amygdala, hippocampus, insula, and VTA (see Ref. 297). As stress also increases drug craving, we examined brain activation during stress and neutral imagery in a functional magnetic resonance imaging (fMRI) study. Although healthy controls and cocaine-dependent individuals showed similar levels of distress and pulse changes during stress exposure, brain response to emotional stress in paralimbic regions such as the anterior cingulate cortex, hippocampus, and parahippocampal regions was greater in healthy controls during stress, while cocaine patients showed a striking absence of such activation.[298] In contrast, cocaine patients had increased activity in the caudate and dorsal striatum region during stress that was significantly associated with stress-induced cocaine craving ratings.

Recent PET studies have also shown significant positive correlations between the dorsal striatum and drug cue–induced cocaine craving.[299,300] These findings are consistent with imaging studies with alcoholic patients showing increased association between dorsal striatum regions and alcohol craving in response to presentation of alcohol-related stimuli.[301,302] Using PET imaging with alcoholics and cocaine patients, research has shown a significant association between dopamine D2 receptor binding in the VS and drug craving as well as motivation for self-administration.[124,303,304] On the other hand, neuropsychological and imaging studies examining prefrontal executive functions, including impulse control, decision making, and set shifting, have shown executive function deficits and hypofrontal responses in addicted individuals compared to control volunteers.[305–312] Together, these findings indicate that increased stress and cue-induced craving and compulsive drug-seeking states in addicted individuals are associated with greater activity in the striatum, but decreased activity in specific

regions of the cingulate and prefrontal cortex and related regions involved in controlling impulses and emotions.

## Stress-Induced Reinstatement of Drug Seeking and Relapse

While several efficacious behavioral and pharmacological therapies in the treatment of addiction exist, it is well known that relapse rates in addiction remain high.[30,313,314] Exposure to stress, drug-related stimuli, and drugs themselves each reinstate drug-seeking behavior in animals and increase relapse susceptibility in addicted individuals.[274,315–317] Such data underscore the need for specific attention to the chronic relapse susceptibility as a target in addiction treatment development.

In the last decade, a substantial number of preclinical studies have shown that brain CRF, noradrenergic, and glutamatergic pathways contribute to reinstatement of drug seeking.[86,316–320] Neuroadaptations associated with chronic drug use include overactive brain CRF and glutamatergic pathways, altered autonomic responses, and underactive dopamine and GABA systems, and these changes may accompany the high craving states and relapse susceptibility associated with the chronic nature of addiction.[118,196,197,274,313,321] Furthermore, using animal models of drug self-administration and relapse, preclinical studies have identified CRF antagonists, alpha-2-adrenergic agonists, and more recently, glutamatergic agents as important in reducing stress-induced seeking in addicted laboratory animals (see[316,317,322–324]). These data are consistent with human findings reviewed in the previous section indicating that alterations in stress and dopaminergic pathways accompany high distress and craving states and blunted physiological and neural responses that are important in regulation of stress, craving, and impulse control.

Human research has also begun to identify markers of the stress and craving states that are predictive of relapse outcomes. To fully understand whether the increased distress and drug-craving state is predictive of relapse, we followed the inpatient treatment-engaged cocaine- and alcohol-dependent individuals in our studies described in previous sections after discharge from inpatient treatment for 90 days to assess relapse outcomes. For the cocaine group, we found that stress-induced cocaine craving in the laboratory significantly predicted time to cocaine relapse. While stress-induced ACTH and cortisol responses were not associated with time to relapse, these responses were predictive of amounts of cocaine consumed during follow-up.[325] While drug cue–induced craving was not predictive of relapse in this study, there was a high correlation between stress and drug cue–induced drug craving and in stress and drug cue–induced HPA responses. These data suggest that at least in the case of cocaine dependence, stress and drug cue–induced distress states produce a similar compulsive drug-seeking state that is associated with relapse vulnerability. In alcoholics, negative mood, stress-induced alcohol craving, and blunted stress and cue-induced cortisol responses have been associated with alcohol relapse outcomes.[236,326–329] Nicotine-deprived smokers who were exposed to a series of stressors showed blunted ACTH, cortisol, and blood pressure responses to stress but increased nicotine withdrawal and craving scores, and these responses were predictive of nicotine relapse outcomes.[289] Thus, for alcoholic and smoking samples, as in the cocaine group, it appears that the drug-craving state marked by increasing distress and compulsive motivation for drug (craving) along with poor stress regulatory responses (altered glucocorticoid feedback or increased noradrenergic arousal) results in an enhanced susceptibility to addiction relapse.

Findings from basic science and human laboratory and clinical outcome studies identify several pharmacological treatment targets to address stress-induced reinstatement of drug seeking and relapse susceptibility. Basic science data suggest CRF antagonists, alpha-2 adrenergic agonists, and glutamatergic agents could be promising in addressing stress-related relapse. Human laboratory studies are needed that will screen these agents to assess their promise with regard to intermediate markers of stress-related relapse susceptibility. Such studies would target

stress- and cue-induced drug craving, craving-related anxiety, HPA measures, and heart rate or heart rate variability as well as responses in specific brain regions.[297] For example, in a preliminary laboratory and clinical outcomes study, we have shown that lofexidine, an alpha-2 adrenergic agonist, significantly decreased stress-induced opiate craving and stress-induced anger ratings, while also improving opiate relapse outcomes in naltrexone-treated, opiate-dependent individuals.[330] Similarly, behavioral strategies that decrease anxiety and stress-related drug craving and normalize stress responses so as to potentiate adaptive responding in high-challenge contexts would be of benefit in decreasing the effects of stress on drug seeking and relapse. For example, mindfulness based stress reduction (MBSR) is efficacious in decreasing relapse to major depression, and adaptations of these strategies could be of benefit to address relapse risk in addiction.[274]

## Summary and Future Directions

This review focuses on the accumulating evidence from preclinical, clinical, and population studies that highly stressful situations and chronic stress increase addiction vulnerability, that is, both risk of developing addiction and risk of relapse. The types of stressors that increase addiction risk are identified in Table 1. The stressors tend to be highly emotionally, distressing events that are uncontrollable and unpredictable for both children and adults. The themes range from loss, violence, and aggression to poor support, interpersonal conflict, isolation, and trauma. There is also evidence for a dose-dependent relationship between accumulated adversity and addiction risk—the greater the number of stressors an individual is exposed to, the higher the risk of developing addiction. Work-related stressors have weaker support, but individual-level variables such as trait negative emotionality and poor self-control (possibly similar to poor executive function) appear to also contribute uniquely to addiction risk. Exposure to such stressors early in life and accumulation of stress (chronicity) result in neuroendocrine, physiological, behavioral, and subjective changes that tend to be long lasting and adversely affect development of brain systems involved in learning, motivation, and stress-related adaptive behaviors. Research that directly addresses stress-related neurobiological changes and their association with behavioral outcomes is sorely needed. Evidence to clarify the contribution of stress to alterations in mesolimbic dopamine activity and its association with drug use is also needed. Figure 1 presents a schematic model of associations that have been supported in research, as well as remaining gaps.

A review of evidence indicating the effects of drug use and abuse on stress responses and dopamine transmission is presented, along with altered emotional and motivational responses associated with craving and relapse to drug use. While substance abuse results in changes in stress and dopaminergic pathways involved in motivation, self control, and adaptive processes necessary for survival, evidence for whether such changes enhance drug seeking or craving and drug use behaviors is lacking. For example, studies on whether prior exposure to licit and illicit drugs modifies the association between stress and drug self-administration are rare. While there are specific neuroadaptations in reward and associated regions, it is also important to examine which of these changes are involved in increasing drug intake and supportive of addictive processes such as progressive loss of control, persistence of craving, and escalating drug self-administration. As stress also increases risk of mood and anxiety disorders that are highly comorbid with addiction, it is important to examine whether there are specific stress-related factors that contribute to risk for mood and anxiety disorders and addiction risk. That is, what are the resiliency factors that are protective for one set of illness but are vulnerabilities for the other. Exploration of gene–environment interactions could be particularly helpful in answering such questions.

A review of recent studies on stress-induced reinstatement to drug seeking, drug craving, and relapse susceptibility is also provided. Clinical implications include the development of new

assessment procedures and markers that will be useful in identifying those who are at particular risk for stress-related relapse and testing of novel pharmacological therapies that target the link between stress and relapse risk. As shown in Figure 2, addicted individuals show enhanced sensitivity to craving and greater anxiety in stress- and drug-related situations, but whether such altered responses represent transitions due to chronic drug use or chronic stress states needs to be further examined. Research on the mechanisms by which chronic stress and drug use alter executive functions that are involved in adaptive behavioral responses is needed. Efficacious behavioral treatments focus on improving coping response. However, stress exposure and chronic distress decrease stress adaptive and coping mechanisms, and hence treatments that focus on enhancing coping may not be suitable for those with stress-related risk factors. Development of new interventions that target self-control, especially in the context of stress is needed. Systematic research on these questions will lead to a greater understanding of how stress is associated with relapse. Furthermore, such research may be significant in developing new treatment targets to reduce relapse, both in the area of medication development and in developing behavioral treatments that specifically target the effects of stress on continued drug use and relapse in addicts.

## Acknowledgments

Preparation of this review was supported by grants from the National Institutes of Health, P50-DA165556, R01-AA13892, R01-DA18219, and U01-RR24925.

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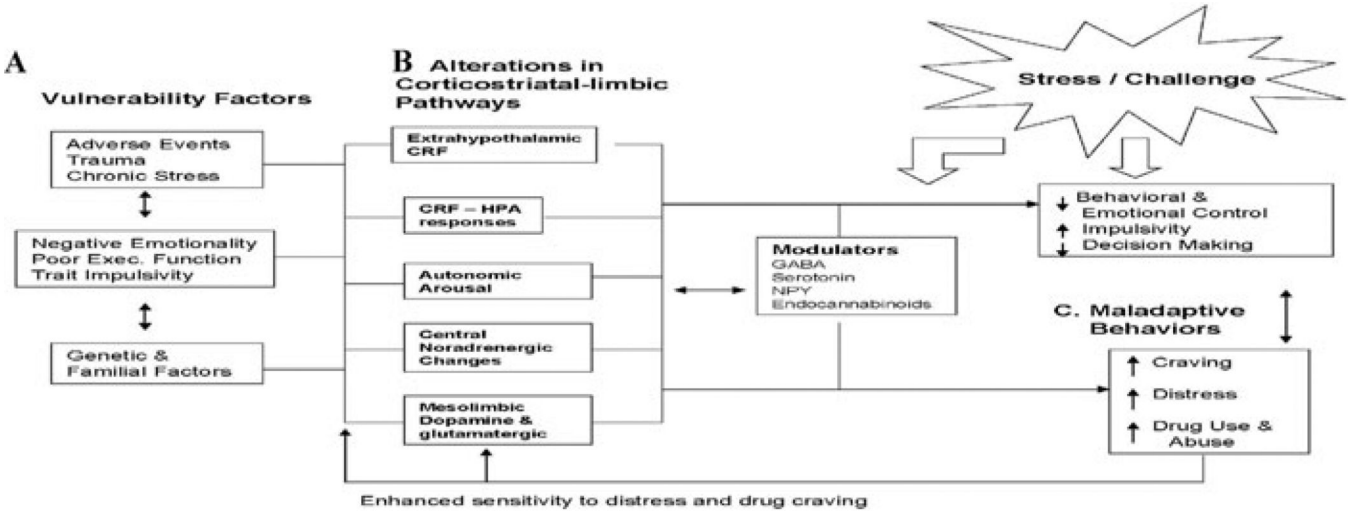


**Figure 1.**

A schematic model of stress effects on addiction, representing the cross-sensitization of stress and drugs on behavioral and neurochemical responses, that are mediated by the stress and reward pathways. Column A lists three types of vulnerability factors: (1) developmental/ individual-level factors such as frontal executive function development, negative emotionality, behavioral/self control, impulsivity or risk taking, and altered initial sensitivity to rewarding effects of drugs; (2) stress-related vulnerability factors such as early adverse life events, trauma and child maltreatment experiences, prolonged and chronic stress experiences; and (3) genetic influences and family history of psychopathology. Each of these factors influences each other to significantly affect alterations in neurobiological pathways involved in stress regulation and cognitive and behavioral control (Column B). Such changes at least partially mediate the mechanisms by which stress and individual and genetic factors in column A interact to increase risk of maladaptive behaviors represented in column C when an individual is faced with stress or challenge situations.

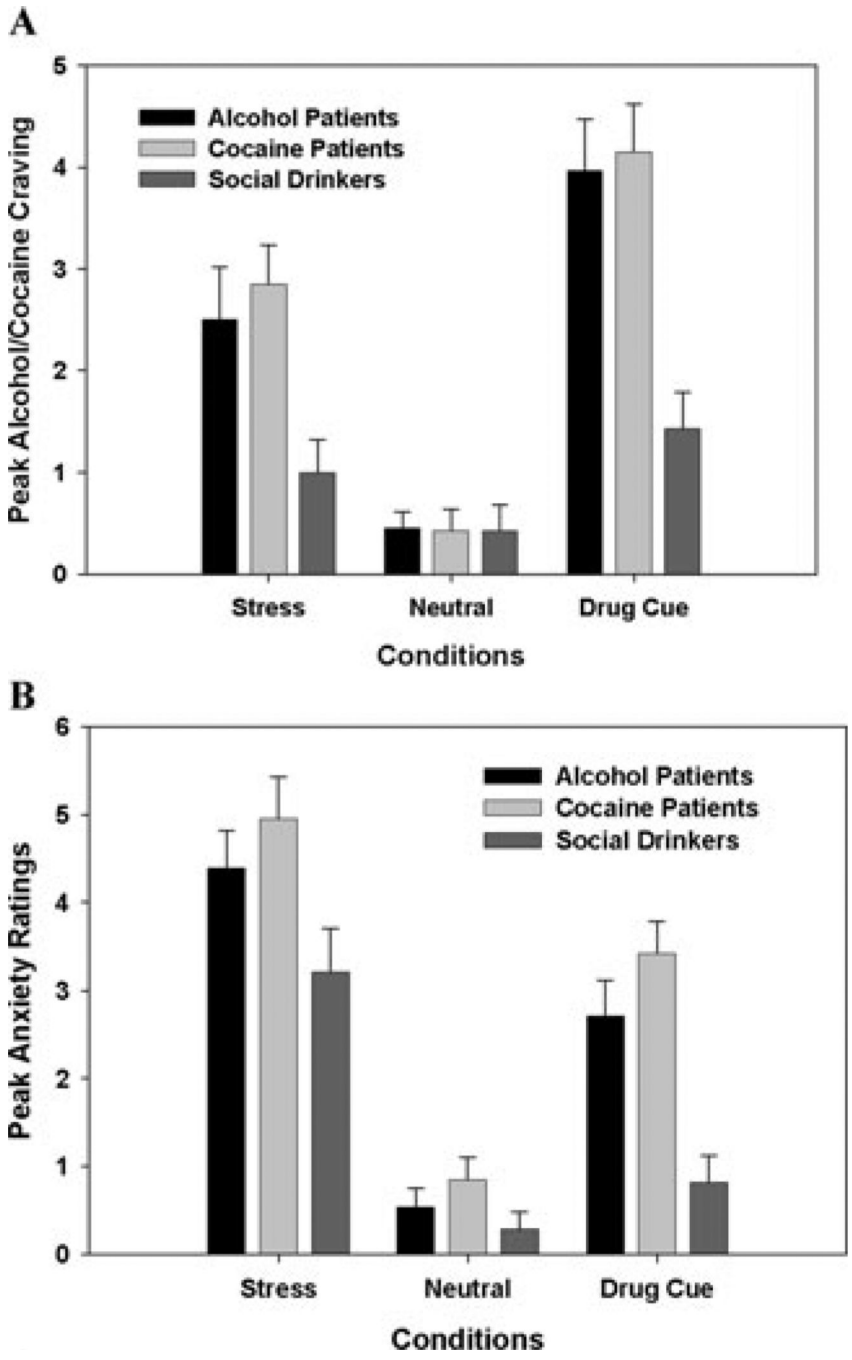


**Figure 2.**

Mean and standard errors for peak craving and anxiety ratings during exposure to stress, drug cues, and neutral imagery conditions. **(A)** Peak craving is significantly higher in abstinent alcoholics and cocaine patients compared to social drinkers ($P < 0.0001$). **(B)** Peak anxiety ratings are significantly higher in abstinent alcoholics and cocaine patients compared to social drinkers ($P < 0.001$). (Detailed statistics provided in Fox *et al*.[291] and Sinha *et al*.[239])

**TABLE 1**

Types of Adverse Life Events, Trauma, Chronic Stressors, and Individual-Level Variables Predictive of Addiction Risk

| | | |
|---|---|---|
| Loss of parent | Physical neglect | Negative emotionality |
| Parental divorce and conflict | Physical abuse by parent/ caretaker/family member/ spouse/significant other | Poor behavioral control |
| Isolation & abandonment | | Poor emotional control |
| Single-parent family structure | Emotional abuse and neglect | |
| Forced to live apart from parents | Sexual abuse | |
| Loss of child by death or removal | Rape | |
| Unfaithfulness of significant other | | |
| Loss of home to natural disaster | | |
| Death of significant other/close family member | | |
| Victim of gun shooting or other violent acts | | |
| Observing violent victimization | | |