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Opinion

Central and Peripheral Biomarkers of Stress Response for Addiction Risk and Relapse Vulnerability

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Substance use disorders (SUDs) are marked by heterogeneity in clinical symptomatology and high relapse rates following treatment. Here, we describe specific peripheral and central stress responses associated with the pathophysiology of SUDs. We outline potential stress response measures, including hypothalamus–pituitary–adrenal axis markers, autonomic responses, and central structural and functional brain alterations that could be exploited as putative biomarkers in SUDs. We posit that stress responses can be predictive of both the development of SUDs and their high relapsing nature. We examine their potential as candidate biomarkers, as well as the remaining challenges in developing and implementing their application for the prevention and treatment of SUDs.

Highlights

Stressful events and stress biology have a critical role in addiction, contributing to its development and high relapsing nature.

The ratio of cortisol:adrenocorticotropic hormone (ACTH), a measure of sensitivity of the adrenal glands to release cortisol in response to the ACTH signal, may emerge as a potent peripheral predictive biomarker of drug dependence, particularly of relapse.

Changes in endogenous neurochemicals, such as brain-derived neurotrophic factor (BDNF), in individuals with a SUD during abstinence, may help predict future relapse.

Individuals with SUDs display basal hyperactivity of central brain and peripheral stress markers and hypoactivity in response to stress and drug cue provocation.

Central and Peripheral Stress System Alterations as Potential Biomarkers of Substance Use Disorders

SUDs present a major public health burden to patients and society in the USA, costing more than US$400 billion annually in crime, poor health outcomes, and lost productivity [1]. Patients with SUDs have significant heterogeneity in clinical symptomatology and vast variability in response to treatment. In SUDs, unlike other psychiatric conditions, certain diagnostic biomarkers exist that may allow for the detection and/or quantification of drugs in the body; this has clear clinical benefit in determining whether a patient has recently used a drug or has been abstinent [2]. While these objectively assessed markers of recent drug use are critical for the assessment of substance use, abuse, and also current diagnosis of SUDs, they are not as informative in identifying who is at risk for developing SUDs or who may be susceptible to a severe clinical course and (consequently) be at risk for treatment failure or relapse [2,3]. Hence, there is an urgent need to characterize objectively measured biomarkers identifying the neurobiological and behavioral processes that lead to the development of SUD disease symptomatology, as well as those that might predict clinical outcome [4]. In turn, identification of these biomarkers could lead to significant improvements in treatment approaches for substance abuse [3]. Here, we present an overview of current knowledge regarding stress-related peripheral and central nervous system (CNS) responses in individuals presenting with, and those at risk for, SUDs; we also assess whether any of these measures could be exploited as SUD biomarkers. We include a discussion on the potential utility as well as the accompanying challenges of putative biomarkers of stress-related altered responses.

Stress and Addiction Risk

Many of the major theories of addiction identify an important role of stress in addiction. These include psychological models that view drug use and abuse as a coping strategy to deal with

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stress, reduce tension, self-medicate, or decrease withdrawal-related distress [5]. In addition, they encompass neurobiological models that propose **incentive sensitization** (see Glossary) and **stress allostasis** concepts to explain how neuroadaptations in stress, **reinforcement learning**, and reward pathways may enhance the key features of addiction (e.g., craving, compulsion, and loss of control over drug intake) [5]. Growing evidence points to the critical role of stress in increasing addiction vulnerability. For instance, population-based and clinical studies have shown a significant association between psychosocial adversity, traumatic exposure, negative affect, chronic distress, and internal deprivation states with addiction risk [6–10] (Table 1). These findings underscore the impact of chronic and repeated exposure to stress and adversity on peripheral and central stress responses, increasing an individual's vulnerability to drug use and abuse, as detailed below.

Autonomic Nervous System and Hypothalamic–Pituitary–Adrenal Axis Responses to Stress

The stress response is triggered by challenging, threatening, overwhelming, or aversive stimuli, and is characterized by neural, physiological, and hormonal changes allowing the organism to cope with the stressor ('fight or flight'), subsequently returning to baseline to maintain homeostasis; this adaptive process is called 'allostasis' [11]. One aspect of the mammalian physiological response to stress is mediated by the hypothalamus–pituitary–adrenal axis (HPA), which comprises the paraventricular nucleus of the hypothalamus, the pituitary gland, and the adrenal gland. Neurons in the paraventricular nucleus synthesize and release corticotropin-releasing factor (CRF) into portal blood vessels entering the anterior pituitary gland. Here, the CRF binds to the CRF1 receptors on pituitary corticotropes, which in turn induce the release of adrenocorticotropic hormone (ACTH) into circulation. ACTH then stimulates the adrenal glands to synthesize and secrete glucocorticoids (corticosterone in rats and cortisol in humans), which mobilize and regulate the stress response of the body (reviewed in [12]). The second pathway involved in the biological response to stress is created by the autonomic nervous system (ANS), namely, the sympathetic and parasympathetic components. The sympathetic component mobilizes arousal by increasing heart rate (HR) and blood pressure; the parasympathetic component enforces the 'brakes' for sympathetic arousal and functions to decrease and regulate the autonomic function [7]. Autonomic pathways also regulate and influence cortisol secretion directly via the splanchnic nerve innervation of the adrenal glands, as well as by interacting with the central component of glucocorticoid activation [3,13].

Growing evidence indicates that the use and abuse of psychoactive substances actively involve these stress arousal pathways, stimulating and activating the HPA and autonomic axis in the case of psychostimulants (cocaine, nicotine, and amphetamine), alcohol, cannabis, and also with certain types of opioids [7]. There may also be significant variation in these responses, as assessed by plasma/serum concentrations of ACTH and cortisol (the latter also in saliva), **salivary alpha amylase** (a measure of autonomic adrenergic arousal), in addition to physiological assessments of HR and **HR variability** (HRV) as a function of the degree of chronic stress or trauma exposure [7,14,15]. These responses to stress and drugs can be modulated by genes encoding HPA axis stress response markers, as well as by epigenetic changes in glucocorticoid signaling genes in response to chronic exposure to stress and adversity [16]. While several studies have linked greater stress reactivity in plasma and/or salivary cortisol as a risk factor for comorbidity of mood disorders and addiction [17–19], research has also shown that blunted salivary cortisol responses to stress in at-risk children with a family history of substance abuse also constituted an addiction risk factor [20,21]. Specifically, one study evaluated at-risk prepubertal (ages 10–12) boys with substance-abusing fathers, and found that high-risk boys secreted significantly less salivary cortisol in response to an anticipated stressor compared with controls [20]. In a recent study, it was demonstrated that 14–17-year-

Glossary

Cold pressor test: cardiovascular test that measures changes in blood pressure and heart rate when a hand is immersed in ice water, typically for 1 min.
Dorsolateral prefrontal cortex (DLPFC): has a role in executive functions in humans and nonhuman primates (e.g., working memory, inhibition, and cognitive flexibility).
Heart rate variability (HRV): measurement of beat to beat changes in heart rate; reflects sympathetic and parasympathetic (autonomic) nervous system activity on cardiac function.
High frequency heart rate variability (HF-HRV): thought to be an index of parasympathetic nervous system activity.
Incentive sensitization: sensitization to the incentive motivational effects of drugs and drug-associated stimuli.
Limbic–striatal-level activation: limbic brain areas include the amygdala, hippocampus, hypothalamus, and insula regions related to emotion and stress responses, while striatal regions include the nucleus accumbens, caudate nucleus, putamen, and globus pallidus, areas involved in reward, habits, learning, and motivation.
Neutral relaxing scenarios: commonly experienced neutral-relaxing situations that do not involve drug use or cues (e.g., sitting at the beach and watching the waves; reading on a Sunday afternoon at the park).
Protracted abstinence: postacute withdrawal period during early abstinence from a drug; it typically includes the period between 1 week to 3 months post last drug use.
Reinforcement learning: learning processes pertaining to positive and negative reinforcement; positive reinforcement pertains to the addition of a reinforcing stimulus following a behavior that makes it more likely that the behavior will occur again in the future; negative reinforcement pertains to removal of an aversive stimulus following a behavior.
Salivary alpha amylase: increased in response to psychological and physical stress through interactions with the autonomic nervous system

olds prenatally exposed to cocaine exhibited elevated basal salivary concentrations of cortisol relative to nonexposed youths; by contrast, they exhibited a blunted salivary cortisol response to specific social stressors compared with controls [22]. Furthermore, this study showed that sex differences were associated with predicting future substance use, where self-reported sadness in girls in response to a stressor could predict future drug use relative to boys; however, in boys, reduced salivary alpha amylase concentrations in response to the same social stressor predicted future drug use, relative to girls [22,23]. This suggested distinct physiological and emotional stress response risk profiles for boys and girls in the context of drug use vulnerability [22,23].

In another series of studies, impaired neuroendocrine responses to alcohol were also associated with an increased motivation for binge and/or heavy alcohol intake, thereby serving as a potential risk marker for the progression from heavy drinking to alcohol dependence [24]. Specifically, in a longitudinal study of heavy drinkers and light drinkers exposed to an oral alcohol challenge with a follow-up of 6 years, heavy drinkers exhibited greater sensitivity to stimulating effects and lower sensitivity to the sedative effects of alcohol compared with light drinkers; moreover, heavy drinkers demonstrated lower salivary cortisol release in response to the alcohol challenge, and presented with a greater number of alcholol use disorder (AUD) symptoms 6 years later, relative to light drinkers [24,25].

A possible mechanism underlying an increased risk for problematic substance use has been documented in children of parents with SUDs, where HR response were measured in response to psychosocial stress in participants (ages 11–20; children with SUD parents versus children with healthy parents) [26]. The at-risk children exhibited a blunted HR recovery to the stress exposure, suggesting that children who are at high risk for developing an SUD are marked by dysregulated ANS responses [26]. In another study, the same group examined the relationship of salivary cortisol concentrations in response to a social stress task with age of onset of alcohol intake in adolescents (aged 14–20 years) [27]. The findings showed that teenagers who began drinking at an earlier age demonstrated lower salivary cortisol at the onset of, and during, the stressful task, relative to teenagers who began drinking when older; this suggested that decreased HPA axis activity in response to stress is present (and significant) in adolescents who begin drinking at an early age [27].

In nonhuman primates, chronic, moderate alcohol exposure in cynomolgus monkeys led to decreased HRV; however, when the animals were exposed to an acute stressor of removal

(ANS); it has been used as a biomarker of ANS activity in various fields of biobehavioral research.
Stress allostasis: adaptive process in response to acute stress aimed at maintaining balance.
Stroop Color/Word Test: evaluates cognitive inhibitory performance; used extensively in both clinical and experimental fields to assess a subject's ability to inhibit incongruent competing conflicts.
Tonic and phasic vagal reactivities: indexed by HRV, and are correlates of self-regulatory function (tonic) and ANS response (phasic).
Ventromedial prefrontal cortex (vmPFC): has a role in the inhibition of emotional responses, decision-making, and self-control.
Voxel-based morphometry (VBM): automated neuroimaging analysis technique that investigates scanned focal differences in brain anatomy, using statistical parametric mapping.

Table 1. Types of Adverse Life Events, Trauma, Chronic Stressors, and Individual-Level Variables Predictive of Addiction Risk[a]

Adverse life event	Childhood and life trauma	Chronic stressor	Stressful internal state
Loss of parent Parental divorce and conflict Isolation and abandonment Single-parent family structure 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 significant other and/or close family member	Physical neglect Physical abuse by parent, caretaker, family member, spouse, and/or significant other Emotional abuse and neglect Sexual abuse Rape Victim of gun shooting or other violent act Observing violent victimization	Being overwhelmed Unable to manage life problems Difficulties with job and/or living situation Financial problems Interpersonal conflicts and/or loneliness Unfulfilled desires Problems with children Illness of loved ones Negative emotionality Poor behavioral control Poor emotional control	Hunger or food deprivation Food insecurity Extreme thirst Sleep deprivation and/or insomnia Extreme hypo- or hyperthermia Excessive drug use Drug withdrawal states Chronic illness

[a]Adapted from [7].

from their home cage to a novel environment, those with a history of alcohol exposure presented higher HRs compared with controls [28].

We do not present a comprehensive review above, but rather, describe a selected set of studies with longitudinal follow-up and predictive validity, to illustrate that moderate levels of drug use exposure, as well as certain types of chronic stress or prenatal drug and/or stress exposure, can impair physiological HPA axis and emotional stress responses in ways that influence the future risk of SUDs. Such adaptations or changes related to drug exposure or chronic stress exposure suggest altered central regulation of peripheral stress pathways. For example, one pathway by which altered central regulation may occur is via altered GABA receptor functioning and other mechanisms known to regulate HPA axis and autonomic responses, possibly increasing addiction risk [29–31]. We posit that these peripheral alterations reflect alterations in central stress regulators and may serve as 'readouts' of central function and could be developed further as risk biomarkers for the development of SUDs. However, it is clear that future research is needed to robustly assess the sensitivity and specificity of stress response markers in separate at-risk groups for their ability to accurately predict drug use initiation, and progression to SUDs. Accordingly, specific central and peripheral stress response measures that may be further explored as potential risk biomarkers are summarized in Table 2 (Key Table).

Key Table

Table 2. Stress Response Disruptions Implicated in SUD Risk, High Relapse Risk, and Treatment Failure[a,b]

Acute	Binge	Chronic/Relapse	Treatment target[c]
Increased cortisol	Decreased cortisol	High basal cortisol	Pexacerfont
		Blunted phasic cortisol	Mifepristone
Increased ACTH	Decreased ACTH	High basal ACTH	Naltrexone
		Blunted phasic ACTH	Neuroactive steroids
		High cortisol:ACTH ratio as relapse predictor	Progesterone
Increased HR	Blunted phasic HR	High basal HR	Doxazosin
		Blunted phasic HR	Prazosin
		Blunted HRV	
vmPFC activation	VmPFC hypoactivity in stress and cue states	VmPFC hyperactivity in neutral states	Guanfacine, progesterone

Biomarker: Risk Predictive Prognostic

[a]These measures may serve as potential biomarkers in acute, binge, and chronic and/or relapse use phases of SUDs and represent potential neurobiological targets for treatment development.

[b]Abbreviations: ACTH: adrenocorticotropic hormone; CRF: corticotropin-releasing factor; HR: heart rate; vmPFC: ventromedial prefrontal cortex.

[c]Treatment targets: pexacerfont, CRF1 receptor antagonist [84]; mifepristone, glucocorticoid receptor antagonist [86]; naltrexone, opioid receptor antagonist [83]; neuroactive steroids, $GABA_A$ receptor agonists [91]; progesterone [90]; doxazosin, α1 adrenergic antagonist [88]; prazosin, α1 adrenergic antagonist [87]; guanfacine, α2 receptor antagonist [89].

Central Brain Response to Stress and Risk of SUDs

Several previous human studies suggest that trauma, adversity, and chronic stress alter the activity and structure of the prefrontal cortical, limbic, and striatal brain networks involved in regulating stress, emotions, reward, and higher cognitive or executive control functions [7]. These functions can include the regulation of distress and emotions, such as controlling and inhibiting impulses, refocusing and shifting attention, working memory, monitoring conflict and behavior, linking behaviors to possible future consequences, and flexible consideration of alternatives for response selection and decision-making [32]. Recent evidence from human brain structural and magnetic resonance imaging (MRI) showed that recent life stressors, such as death in the family, divorce, relationships ending, assault, financial crisis, robbery, trauma (physical, emotional, and/or sexual abuse) as well as chronic stress (subjective experience of continuous stressors or ongoing life problems), are associated with lower gray matter volume in medial prefrontal, amygdala, hippocampus, and insula regions of the brain [33,34] (Table 1). Similarly, recent life stress and acute stress exposure (Table 1) may decrease responses in the prefrontal regions, such as the **dorsolateral prefrontal cortex** (DLPFC) and **ventromedial prefrontal cortex** (vmPFC) (associated with working memory, reward processing, and resilient coping), might be linked to at-risk drug use and emotional dysregulation, such as binge alcohol intake, emotional eating, and frequency of argumentation and/or fighting [35]. Thus, with increasing levels of stress, functional (f)MRI has indicated decreased prefrontal functioning and increased **limbic–striatal-level activation**, brain patterns associated with low behavioral and cognitive control [35]. In another study, prenatally cocaine-exposed 14–17-year-old adolescents exhibited lower gray matter volume in limbic and frontal regions of their brains, as assessed by MRI and whole-brain **voxel-based morphometry**, relative to noncocaine-exposed adolescent controls; moreover, lower gray matter volume in these brain regions was associated with substance use initiation [36], thereby suggesting that changes in brain volume serve as biological risk markers of substance use. Indeed, low behavioral and cognitive control linked to reduced prefrontal and insular cortex activity, as well as the high activation of limbic–emotional and striata–motivation brain regions under stress, suggest specific patterns that underlie a risk for developing addictive behaviors concomitant with a decreased ability to control rewarding behaviors [37]. Thus, motivational brain pathways appear to be key targets of disrupted central stress activity that suggest a potentially important mechanism where stress could affect susceptibility to addiction. Nevertheless, these potential pathways and targets need further assessment in future studies to identify specific measures that, upon validation, might be used as candidate risk biomarkers of SUDs.

Chronic Drug Abuse Alters Stress Responses: Potential Predictors of Increased Drug Motivation and Candidate Biomarkers

The HPA Axis: Cortisol and ACTH in Drug Abuse Motivation

In humans, enhanced stress-system activity has been associated with chronic smoking as well as with cocaine and alcohol consumption [38,39]. Elevated basal plasma and salivary cortisol levels have been observed with active binge alcohol intake and recent withdrawal from alcohol in alcohol-dependent individuals [40–43]. Lower basal plasma ACTH levels have been found in individuals with a high risk for alcoholism based on family history, compared with low-risk individuals [44]. Moreover, markedly reduced ACTH and cortisol concentrations in response to both pharmacological stimulation of the HPA axis with human corticotrophin-releasing hormone (CRH) and psychosocial stressors (e.g., mental arithmetic, **cold pressor test**, or interpersonal conflict) have also been reported in chronic alcohol abusers compared with controls [41,45–49]. Similarly, cigarette smoking has been shown to elevate circulating plasma ACTH and cortisol in moderate smokers [50,51]; furthermore, decreased plasma and salivary ACTH and cortisol in response to psychosocial stress (public speaking or mental arithmetic)

have been reported in smokers during withdrawal relative to sham smokers [52]. The stress-induced and drug or alcohol cue-induced craving state in patients with SUD has been characterized during **protracted abstinence**; the findings indicated that these cravings were accompanied by enhanced negative emotion and anxiety as well as by altered plasma cortisol and ACTH concentrations in early-abstinent cocaine abusers [53,54], comorbid cocaine and alcohol abusers [55], as well as in early-abstinent alcoholics relative to controls [56–58].

Together, these findings suggest that regular binge use of psychoactive substances, such as nicotine, alcohol, and cocaine, alters physiological stress pathways; such alterations are accompanied by a greater motivation to use drugs, and with higher levels of drug use. Thus, we posit that, upon further assessment, chronic drug-related stress changes in peripheral stress neuroendocrine function may serve as putative biomarkers that could reveal the transition from controlled to compulsive drug seeking across a range of substances.

The Autonomic System: Heart Rate and Heart Rate Variability in SUDs and during Drug Use Motivation

In addition to HPA axis dysregulation, chronic drug use can also lead to dysregulation of the ANS. In a recent study, inpatient treatment-engaged, recovering cocaine- and alcohol-dependent individuals completed research participation in 3-day controlled experimental studies where they were exposed to stress, drug cues, or an active neutral relaxing control cue by using standardized personalized guided imagery [59]. Drug craving, anxiety, HR, blood pressure, and several neurochemicals, including plasma cortisol and ACTH and other parameters, such as serum brain-derived neurotrophic factor (BDNF), plasma neuropeptide Y (NPY), and immune cytokines, were measured [3,57,60,61]. Plasma interleukin 6 (IL6), IL-10, IL-1 receptor antagonist (IL-1ra), and tumor necrosis factor alpha (TNFα) concentrations were altered in individuals with SUDs compared with healthy controls [92,93]. NPY expression was reported to be lower in response to stress in the plasma of individuals with SUD compared with healthy controls, and the lower stress-related NPY was predictive of greater relapse severity [94]. Moreover, early abstinent individuals with SUDs displayed persistent high basal HRs [57], and reduced HR responses to the stress imagery conditions relative to healthy controls [3,57,60,61].

One of the first studies to experimentally examine the role of autonomic reactivity in stress-induced craving in nicotine-dependent 15-h-abstinent smokers reported that blunted stress-induced **high-frequency HRV** (HF-HRV) was associated with less time to initiate smoking and increased craving relief and reinforcement from smoking [62]. Recent work examined HRV in nicotine- and alcohol-dependent individuals compared with age-matched controls, and found that HRV was globally decreased in the addicted subjects [63]. Collectively, these data suggest that alterations in HR and HRV can result from chronic drug abuse and, pending further testing, these measures might serve as candidate prognostic biomarkers of treatment course, severity of illness, and relapse risk in SUDs. Furthermore, they might also be useful as predictive biomarkers of treatment outcome; for example, by assessing treatments that aim to normalize **tonic and phasic vagal reactivities** in early-abstinent individuals with SUDs, it may be possible to improve cessation and abstinence outcomes. However, these possibilities remain to be tested.

Central Brain Response in Drug Abuse Motivation

Chronic stress states and substance abuse each result in altered neuroadaptive function in the prefrontal–striatal limbic circuits [37]. Human neuroimaging studies using fMRI have shown that hyperactivity in the limbic–striatal regions are associated with not only elevated levels of emotional distress, but also stress-induced drug craving, specifically related to the striatal

region (right caudate and thalamus) and with decreased neuronal activity in the right anterior cingulate cortex (ACC) [64,65]. Additionally, subjective experience of emotional distress has been associated with heightened limbic activity in conditions of social isolation stress [66], as well as with hyperactivity in the amygdala during the experience of negative emotion, (e.g., fear or sadness) [67]. These findings suggest that heightened or sensitized striatal responses under stress and drug cues underlie increased drug-craving states in addiction.

Given that previous work demonstrated that stress-induced and drug cue-induced craving is significantly greater in addicted individuals than in controls [57], researchers also assessed brain correlates of stress and cue-induced alcohol craving in abstinent, treatment-engaged alcohol dependent individuals [68]. The findings indicated robust brain hyperactivity in fMRI during the neutral relaxed state in the ventral striatum and the vmPFC/ACC, correlating with provoked personalized, guided imagery of stress-induced, and cue-induced, alcohol craving [68]. Furthermore, the data identified neuroadaptations in the vmPFC, ventral striatum, and insula networks, documenting disrupted functioning in the relaxed state as well as reduced activity during provoked or challenge conditions (e.g., stress or alcohol cues) in addicted individuals relative to healthy controls [68]. These findings suggest that prefrontal brain regions important in controlling emotions and reward and/or pleasure circuits are altered in chronic alcohol and cocaine use relative to controls. We discuss below whether these measures can serve as predictive biomarkers of SUDs.

Altered Stress Responses Predicting SUD Relapse

SUDs are chronic and relapsing in nature and clinical treatment studies suggest that more than two-thirds of individuals with SUD relapse within weeks to months of initiating treatment [69,70]. Given that relapse rates are high, recent research has focused on whether there is a biology underlying relapse susceptibility and, if so, whether there are specific biobehavioral markers of relapse risk that may be targeted to develop new treatments for relapse prevention. While clinical studies have repeatedly shown that stress is associated with relapse [61], the underlying mechanism in this relationship is not clearly understood. Below, we present evidence that alterations and dysregulation in the HPA axis and other neuropeptides, as well as ANS changes in individuals with SUDs, may be able to predict drug relapse.

The HPA Axis: Cortisol and Cortisol:ACTH Ratio in SUD Relapse

Enhanced stress-related plasma cortisol levels have been associated with relapse factors in cocaine abusers [71], and reduced cortisol production in response to stress has been associated with a shorter time to future relapse in alcoholics [72] and in male smokers [73]. As previously discussed, inpatient treatment-engaged, recovering cocaine- and alcohol-dependent individuals were exposed to personalized, guided stress, drug cues, and **neutral relaxing scenarios** and evaluated for drug craving, anxiety and stress responses (as assessed by ANS and HPA axis markers); individuals with SUDs in early stages of abstinence (28 days), exhibited persistently high basal concentrations of plasma ACTH and salivary cortisol, as well as higher basal HR [57] relative to healthy controls. However, these abstinent individuals presented blunted plasma ACTH, salivary cortisol, and HR responses when presented with stress challenges, relative to controls [3,57,60]. Moreover, after completion of the laboratory study, the patients were discharged from inpatient treatment and observed repeatedly for 90 days to assess future relapse outcomes. For the cocaine group, where altered stress responses were noted compared with controls (see above [60]), higher stress-induced ACTH and cortisol concentrations were not associated with time to relapse, but these responses were predictive of greater amounts of cocaine consumed during follow-up [71]. Abstinent, treatment-engaged, alcohol-dependent individuals with high cortisol:ACTH ratios (a measure of the

sensitivity of the adrenal glands to release cortisol in response to the ACTH signal) were more likely (more than double the risk) to relapse more quickly than those with low cortisol:ACTH ratios after discharge from inpatient treatment [3]. In nicotine-dependent individuals in early abstinence, other research has also shown that blunted cortisol responses may be able to predict early relapse [52,74]. Collectively, stress and cue exposure can lead to persistent negative emotion-related cravings in abstinent individuals with SUDs, in addition to altered HPA axis and physiological arousal responses [57,60].

Growth Factors in SUD Relapse: The Role of BDNF

Evidence from rodent preclinical studies has implicated BDNF in drug-seeking behavior. Specifically, cocaine-related increased BDNF concentrations and signaling (as well as other growth factors) in the CNS of rats have been observed (nucleus accumbens) [75]. Blocking BDNF reduced cocaine self-administration and attenuated relapse behaviors. Moreover, increased BDNF was also associated with reinstated cocaine-seeking behavior in mouse models of cocaine relapse, where BDNF was deemed necessary to maintain increased cocaine self-administration [75]. A human study revealed that morning serum BDNF concentrations were significantly higher in abstinent cocaine abusers [76]. These concentrations were predictive of shorter time to cocaine relapse and higher amounts of cocaine used, as well as greater number of days of cocaine use over a 90-day follow-up in the cocaine-dependent subjects [76].

Central Brain Response in Drug Abuse Relapse

Previous work has revealed that cocaine-dependent individuals, compared with healthy controls, display altered fMRI activation in prefrontal–limbic–striatal circuitry involved in stress, emotion, and reward processing as well as in the regulation of stress responses [64]. Moreover, altered function in these brain regions in cocaine-dependent individuals has been associated with stress-induced and drug cue-induced craving and with an increased risk for future relapse [77]. Specifically, increased activity in the medial PFC has been associated with a shorter time before cocaine relapse occurs, correlating with higher numbers of days of cocaine use during the 90-day period in cocaine-dependent individuals [77].

In addition, a previously discussed fMRI study in abstinent alcohol-dependent individuals reported robust hyperactivity during the neutral relaxed state in the ventral striatum and the vmPFC/ACC relative to controls, correlating with provoked stress-induced and cue-induced drug craving [68]. Noteworthy, the stress- and drug cue-induced craving triggers were also associated with blunted responses in these brain regions in subjects under stress and drug-cue conditions; furthermore, both hyperactivation of the vmPFC in the neutral, relaxed state, as well as hypoactivation of the vmPFC and the insula during stress, were predictive of the amount of future time before alcohol relapse, as well as of the severity of alcohol relapse during the subsequent recovery period [68]. This work was furthered by assessing the relationship between central and peripheral nervous system markers in stress responsivity, and their combined effects on relapse risk [78]. Craving, high basal sympathetic activity, and HPA adrenal sensitivity were significantly associated with vmPFC hypoactivity following exposure to stress [78]. This disrupted vmPFC activation in neutral and stress conditions, sensitively and specifically predicting a shorter time to future relapse. Furthermore, the disrupted neutral state VmPFC function was found to mediate the relationship between adrenal sensitivity and future relapse risk [78].

Other studies have shown that structural alterations in the brains of individuals with SUD exist and may serve as potential markers of relapse risk. For example, in a combined structural and functional MRI study with 46 detoxified alcohol-dependent patients, subsequent relapsers

displayed greater atrophy in the bilateral orbitofrontal cortex (OFC), the right medial PFC, and ACC compared with healthy controls and alcohol dependent patients who remained abstinent [79]. In another MRI study with 75 treatment-seeking alcohol-dependent subjects, relapsers exhibited global reduction in cortical thickness in most brain regions compared with healthy controls [80]. These structural imaging studies suggest that gray matter atrophy in specific stress regulatory brain regions has an important role in alcohol relapse risk.

Based on these above findings, we present a heuristic model in Figure 1 to illustrate the notion that, with higher levels of drug use, there are progressive alterations in stress and cue-related peripheral and central responses, including greater levels of drug motivation and craving accompanied by a drive for compulsive drug use. Parallel brain adaptations in stress circuits with increasing levels of drug history and exposure have also been shown with specific types of structural change and disrupted function, and have been considered to be predictive of future drug use and relapse (Figure 1) [81].

In summary, taken together, these findings support the idea that chronic drug use alters peripheral and central brain stress pathways. There is accumulating evidence that such changes are not nonspecific consequences of chronic drug use, but rather, represent specific alterations that may have a role in compulsive motivation and drug craving, and may enable the

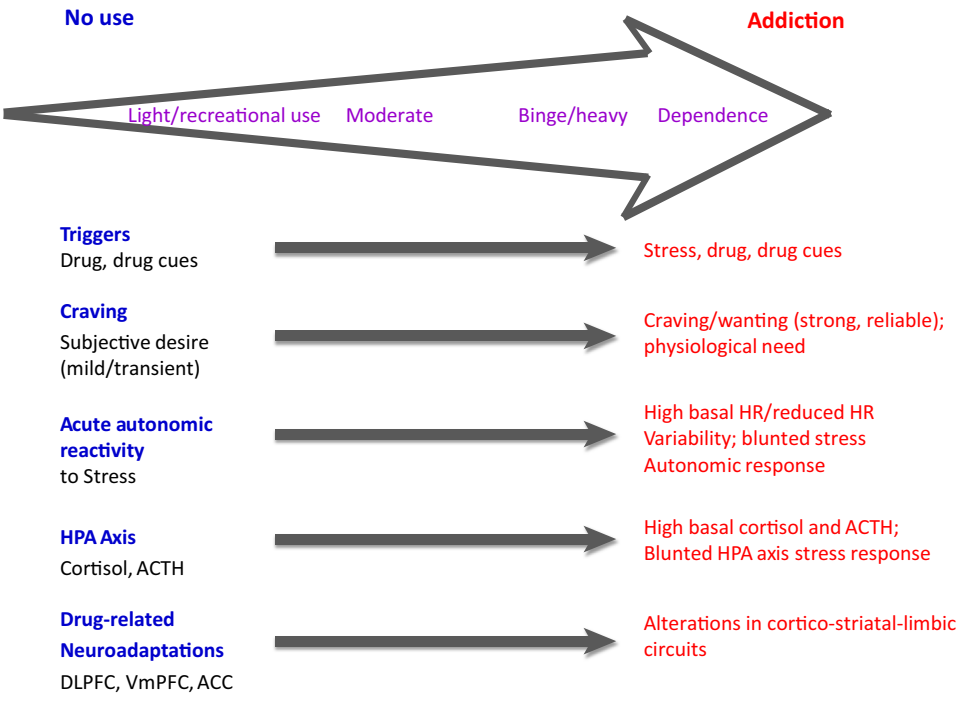

Figure 1. Progressive Changes in Behavioral, Peripheral, and Central Nervous System Stress Responses during Addiction. The schematic diagram represents a model (in individuals with substance use disorders; SUDs) for the observed progressive changes in physiological stress responses, drug motivation and craving, as well as altered stress and drug cue reactivity in parallel to brain responses, as a function of increasing level of drug history and exposure. Abbreviations: ACC, anterior cingulate cortex; ACTH, adrenocorticotropic hormone; DLPFC, dorsolateral prefrontal cortex; HPA, hypothalamus–pituitary–adrenal axis; HR, heart rate; vmPFC, ventromedial prefrontal cortex. Adapted from [81].

prediction of relapse and treatment outcomes. Altered specific markers which have been implicated in predicting future drug use and relapse are summarized in Table 2, and which could be further characterized as putative biomarkers associated with different phases of SUD risk and relapse.

Potential Predictive Biomarkers Relating to Treatment Targets

As previously discussed, recent findings aim to identify objective and sensitive peripheral and central stress response measures that may serve as biomarkers of addiction risk and relapse. Evidence from population-based and clinical studies presented suggest that trauma, adversity, and chronic stress can increase addiction vulnerability, and that chronic psychoactive drug use is associated with dysregulation of the HPA axis and decreased prefrontal executive control over stress and reward pathways. Such altered stress responses may be predictive of increased drug craving and higher risk for future relapse. However, developing and validating these disrupted stress-related biobehavioral measures as biomarkers requires specific and robust attention. Table 2 summarizes the nature of select stress disruptions related to SUD risk and relapse outcomes, as well as the potential for biomarker development at specific stages of SUD. It remains to be determined which of these measures may represent valid biomarkers with high specificity and sensitivity to predict SUD risk and relapse, as well as treatment failure; their use may also vary based on sex, race, age, and also individual genetic and environmental vulnerabilities, and these parameters need to be assessed and established. Of note, the individual differences in adaptations as a result of the disruptions listed in Table 2 have been expected and documented and, consequently, support their future exploration leading to potential biomarkers of SUDs. For example, individuals with prior significant trauma and post-traumatic stress with cigarette smoking and history of alcohol dependence may show reduced HRV, while those without these synergistic risk factors might not [14]. This suggests that multilevel diagnostic, clinical history, biological responses, and genetic and epigenetic vulnerabilities using 'big data' approaches are needed to develop multifactorial risk groupings that link to specific biomarkers of SUD risk.

Based on the evidence presented, it is clear that drug abuse alters peripheral and central stress responses. This begs the question of whether such measures may serve as prognostic biomarkers in treatment development. Given the heterogeneity of stress- and drug-related adaptations, it will be important to identify subgroups of patients with SUD with specific disrupted stress measures (or biomarkers) that might be predictive of drug intake or relapse. Once identified, these biomarkers may be utilized to test different treatment strategies to normalize responses and assess improved disease outcome (Table 2 and Box 1). Such an approach has been used aiming to treat several types of cancer, but for SUD treatment, it remains in its infancy. Moreover, whether normalizing these specific stress disruptions and stress-induced cravings leads to improved treatment outcomes is yet to be established. As discussed, various pharmacological molecules have been tested in preclinical studies of addiction that are active in the peripheral and central stress responses, but their assessment thus far has not incorporated utilizing stress response biomarkers for sample selection. Thus, we suggest that stress response biomarkers that can identify putative key targets for intervention be further evaluated and exploited for clinical utility in SUD treatment approaches.

Concluding Remarks

This opinion provides a targeted summary of altered peripheral and central stress arousal responses in individuals at-risk for addiction and those with SUDs, relative to control volunteers, with specific emphasis on whether these measures are predictive of future drug use, abuse,

Outstanding Questions

Which of the disrupted HPA axis and decreased prefrontal control measures may be used as biomarkers with highest specificity and sensitivity in predicting SUD development, risk of relapse, and treatment outcomes?

What is the influence of sex, race, age, and also individual-level genetic and environmental factors in the disruption of the HPA axis, ANS, and brain activity observed during the development of addiction?

Can these stress biobehavioral measures serve as prognostic biomarkers for treatment?

Given that heterogeneity exists in SUDs, in addition to stress- and drug-related adaptations, can subgroups of patients with SUD be identified with a select combination of the discussed disrupted central and peripheral stress response measures, or other biomarkers that may emerge? Could these in combination provide more accurate predictive, prognostic, and risk biomarkers of SUDs?

Box 1. Targeting Stress Responses in SUD Treatment Approaches

Medication or behavioral interventions that improve vmPFC function and also normalize HPA axis function, (i.e., reduce basal overactivity and reinstate normal phasic stress responses) may improve treatment outcome in individuals with SUDs and reduce relapse risk [82]. For example, naltrexone treatment can increase cortisol concentrations at baseline and decrease drug-related alcohol craving, while increasing alcohol-stimulated ACTH and cortisol responses compared with placebo in nontreatment-seeking individuals with AUD [83]. Thus, naltrexone can reduce alcohol-related neuroendocrine tolerance and improve the effects of alcohol tolerance to stimulate the HPA axis, thereby reducing the blunted alcohol response of the HPA axis. However, these findings have also indicated that naltrexone can increase basal HPA axis tone and tonic cortisol levels relative to placebo, an effect that might be detrimental to individuals with AUD with higher subclinical and clinical HPA axis alcohol withdrawal and/or abstinence pathophysiology [83]. This aspect of naltrexone may render it unsuitable for all individuals with AUD, and may contribute to explaining its modest efficacy in AUDs [83].

CRF antagonists, such as pexacerfont (which directly acts on the stress axis), have been found to reduce ACTH and increase cortisol responses to stress in anxious alcoholic patients [84]. Negative results in this study, and with other CRF receptor antagonists, have been observed with regard to efficacy in reducing alcohol craving responses [84,85]. However, the patient samples were not selected because of a specific alteration in biomarker and/or stress responses. Thus, future research is needed to understand whether CRF antagonists may be targeted to specific subgroups of patients and whether these might be exploited as prognostic biomarkers of high relapse risk.

Recent studies have manipulated central glucocorticoids with mifepristone to normalize peripheral HPA axis responses; the drug was useful in helping to decrease alcohol intake in alcohol-dependent individuals [86]. Noradrenergic compounds that have central effects on ANS, HPA axis, and prefrontal stress pathways have also been examined. For example, the α1-antagonist prazosin was found to reduce stress-induced alcohol craving and negative emotions, while reducing basal cortisol and increasing stress-induced cortisol in alcohol-dependent inpatients during early abstinence [87]. Similarly, the α1-adrenergic antagonist doxazosin reduced cocaine use and improved abstinence outcomes in treatment-seeking cocaine-dependent individuals [88]. The α2-agonist guanfacine was reported to reduce cue-induced craving, decrease baseline cortisol, and normalize stress-induced cortisol in early-abstinent cocaine- and alcohol-dependent individuals [89].

Progesterone administration in treatment-seeking cocaine-dependent men and women has also been examined, indicating that progesterone can lead to reduced cue-induced cocaine craving and cortisol responses and improve prefrontal inhibitory function relative to placebo (as evidenced from the **Stroop Color/Word Test)** [90]. Similar effects with GABAergic neuroactive steroids have been documented, where cocaine- and alcohol-dependent individuals receiving progesterone were grouped based on baseline concentrations of progesterone-derived neuroactive steroid allopregnanolone (ALLO) [91]. The high ALLO group demonstrated reduced craving and improved cognitive performance compared with the low ALLO group, as well as leading to both reduced basal, and increased cortisol in response to stress [91].

and/or relapse. Although many questions remain (see Outstanding Questions), we propose that stress responses linking SUD risk and relapse merit further development as candidate biomarkers of stress-specific measures. Future studies should focus on validating stress biomarkers that specifically relate to loss of control of drug intake (risk) and relapse (predictive), in addition to those that may lead to assessing SUD prevention and treatment outcomes (prognostic), and that may also reduce risk of SUDs (Box 2).

Box 2. Clinician's Corner

Both stress and various drugs of abuse stimulate sympathetic arousal and activate the HPA axis, releasing ACTH and cortisol responses, and eliciting specific response patterns that may be predictive of addiction risk.

Other neurochemicals, such as BDNF and NPY, in plasma have been associated with SUD relapse measures.

With both chronic stress and chronic drug use, peripheral stress systems become dysregulated, with simultaneous disruptions in brain cortico–striatal–limbic circuits, and select changes can be predictive of future addiction relapse risk.

Disclaimer Statement

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