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Drug-induced stress responses and addiction risk and relapse

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ABSTRACT

A number of studies have assessed the effects of psychoactive drugs on stress biology, the neuroadaptations resulting from chronic drug use on stress biology, and their effects on addiction risk and relapse. This review mainly covers human research on the acute effects of different drugs of abuse (i.e., nicotine, cannabis, psychostimulants, alcohol, and opioids) on the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system (ANS) responses. We review the literature on acute peripheral stress responses in naïve or light recreational users and binge/heavy or chronic drug users. We also discuss evidence of alterations in tonic levels, or tolerance, in the latter relative to the former and associated changes in the phasic stress responses. We discuss the impact of the stress system tolerance in heavy users on their response to drug- and stress-related cue responses and craving as compared to control subjects. A summary is provided of the effects of glucocorticoid responses and their adaptations on brain striatal and prefrontal cortices involved in the regulation of drug seeking and relapse risk. Finally, we summarize important considerations, including individual difference factors such as gender, co-occurring drug use, early trauma and adversity and drug use history and variation in methodologies, that may further influence the effects of these drugs on stress biology.

1. Introduction

Substance use disorders (SUDs) incur a significant burden to society in the United States and worldwide. In the United States alone, SUDs are estimated to cost $400 billion across a variety of domains, including crime, poor health outcomes, and lost productivity (US Department of Health and Human Services, 2016). There have been alarming shifts in the clinical presentation where young people are increasingly experiencing more consequences from use as demonstrated by the increases in alcohol-related liver disease (Tapper and Parikh, 2018), opioid use disorder (Martins et al., 2017), and marijuana-related vehicle crashes (Brady and Li, 2014). These trends collectively point to the importance of targeting specific mechanisms that may facilitate the transition from occasional use to chronic, problematic substance abuse.

Early life stress and cumulative adversity, including child maltreatment, are key factors that play a critical role throughout the cycle of addiction, from the development of addictive disorders, to maintenance, relapse, and recovery from SUDs (Enoch, 2011; Le Moal and Koob, 2007; Sinha, 2008, 2001). There has been limited focus on the potent effects of drug use itself on the acute stress response. Although several studies have pointed to an altered setpoint in these systems, less has focused on effects of these adaptations on cue reactivity, drug motivation, and relapse risk. For this reason, we uniquely focus on the effects of acute and chronic drug use on the biological stress pathways and their related effects on stress, reward, craving, and relapse risk. Previous work has investigated the acute effects of different drugs of abuse in animal models of acute and chronic use (Armario, 2010) and translational research on addiction course (Lijffijt et al., 2014). Thus, we focus primarily on human studies and the peripheral stress response and include central reward and motivation pathways when discussing the effects of altered peripheral stress biology on drug motivation and intake. Furthermore, this review covers the most commonly used drugs of nicotine, alcohol, cannabis, psychostimulants (i.e., cocaine and amphetamines), and opioids.

1.1. Relationship between peripheral and central neuroadaptations to drug use

The most frequently studied biological stress responses in relation to SUDs include the two branches of the peripheral autonomic nervous system (ANS), specifically the physiologic responses of the sympathetic and parasympathetic arms, and the neuroendocrine responses of the hypothalamic-pituitary-adrenal (HPA) axis (see Milivojevic and Sinha, 2018 for review of stress biomarkers). For this review, we will focus on specific measures of ANS (i.e., epinephrine/norepinephrine, heart rate variability [HRV]) and HPA axis responses (i.e., adrenocorticotropic

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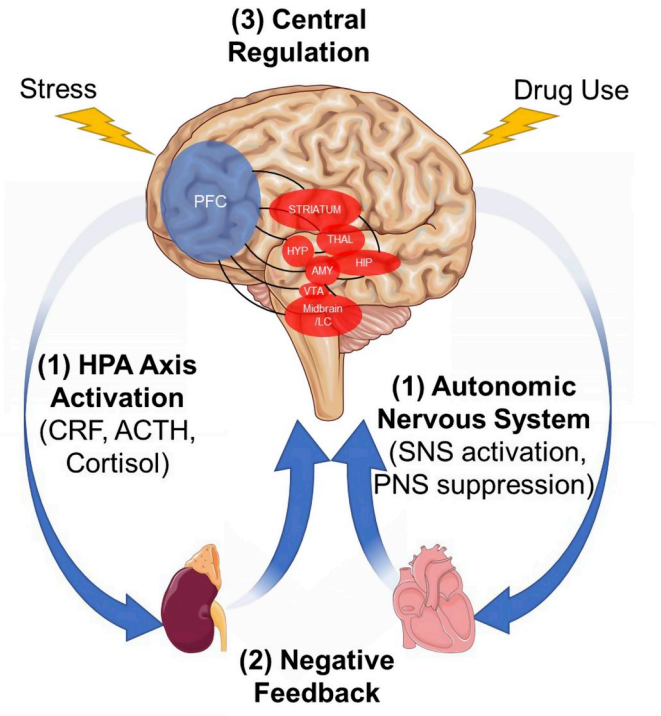

Fig. 1. The dynamic interplay between peripheral stress response and central stress circuitry. Autonomic and HPA axis arousal (1) occurs in response to stress and drug use. This arousal causes a peripheral feedback (2) into limbic circuits as well as central activation to initiate adaptive emotional, cognitive and behavioral responses to regulate stress, emotion and reward states (3). Sensory regions provide information to the amygdala, hippocampus, and locus coerulus (LC), which facilitates adaptation to central emotional, cognitive, behavioral responses. AMY = Amygdala, HP = Hippocampus, HYP = Hypothalamus, PFC = Prefrontal Cortex, THAL = Thalamus, VTA = Ventral Tegmental Area. Templates were used from Servier Medical Art (www.smart.servier.com).

hormone [ACTH], cortisol/corticosterone; see Fig. 1 for an illustration). The central stress pathways in humans have been described in detail in previous reviews (Lovallo, 2006; Sinha, 2008) and include interactions between brain stem (Locus Coeruleus [LC]; Ventral Tegmental Area [VTA]; Substantia Nigra [SN]; Dorsal Raphe), limbic (hypothalamus, amygdala, thalamus, and the Bed Nucleus of the Stria Terminali [BNST]), striatal (ventral and dorsal) and the insular, anterior cingulate and regions of the prefrontal cortex (PFC), and the sensory and motor cortices, circuits that are involved in the processing of drug and stressful stimuli and in regulating these responses (see Fig. 1). These central stress pathways have been most commonly implicated by neuroimaging tools in acute drug effects, drug motivation and as risk markers for relapse (Goldstein and Volkow, 2002; Longo et al., 2016; Sinha, 2013, 2008; Sinha and Li, 2007).

2. Acute and chronic psychoactive drug effects on peripheral stress responses

2.1. Nicotine

2.1.1. Acute effects of nicotine in non- and light smokers

The acute effects of nicotine on the HPA axis in non-smokers or light smokers ("chippers") have not been as well-documented, particularly in human samples, as compared to chronic users. Nevertheless, consistent with evidence in non-dependent animals, nicotine increases corticosterone levels particularly at high levels of nicotine dosing (Acri, 1994; Chen et al., 2008; Donny et al., 2000; Lutfy et al., 2012; Okada et al., 2003). Both nicotine-naïve and regular nicotine users show dose-dependent increases in cortisol, ACTH and prolactin have been reported (see Mello, 2010 for review). Studies of the mechanism in animal models suggest that the effect of nicotine on the HPA axis is primarily through the nicotine-induced release of norepinephrine and CRH in the paraventricular nucleus of the hypothalamus (Fu et al., 1997; Matta et al., 1990; Okada et al., 2003). These collective findings indicate nicotine activates the HPA axis via its direct effects on the catecholaminergic and cholinergic stimulation of the ANS.

Regarding the ANS, naïve or light smokers' catecholamine response has been mostly documented in animal models, but several human studies have studied the cardiovascular effects of nicotine in non-smokers. Epinephrine has been reliably shown to increase in a dose-dependent fashion in response to nicotine (Grunberg et al., 1988; Mello, 2010; Morse, 1989; Watts, 1960), particularly under conditions of nicotine self-administration (Donny et al., 2000). Nicotine also increases cardiovascular output in animals (Watts, 1960), a finding that has been replicated in non-smoking humans (Foulds et al., 1997; Perkins et al., 2009). In human models, several studies have demonstrated that nicotine increases cardiovascular activity as measured by increases in low frequency (LF; an index of sympathetic activity), and decreases in high frequency (HF; parasympathetic activity) HRV, both in response to nicotine and when co-administered with a stressor (Karakaya et al., 2007; Sjoberg and Saint, 2011).

2.1.2. Acute effects of nicotine in chronic, heavy smokers

Chronic nicotine administration dysregulates tonic levels of the HPA axis. Chronic smokers show greater basal cortisol levels relative to non-smokers (al'Absi, 2006). In chronic users, acute nicotine administration further increases cortisol and ACTH levels (Chen et al., 2008; Mendelson et al., 2008; Pomerleau and Pomerleau, 1990; Seyler et al., 1984; Wilkins et al., 1982) in a dose-dependent manner (Hill and Wynder, 1974; Mendelson et al., 2005). Animal models show that nicotine elevates corticosterone and ACTH early in use but, although nicotine still induced a rise, this response to nicotine was attenuated after successive administration (Chen et al., 2008); a comparison that has been replicated in a correlation study of humans where chronic users are compared to chippers (Shiffman et al., 1992). Nicotine withdrawal is associated with a higher basal HPA axis tone and blunted response to nicotine at varying lengths of acute abstinence (Cohen et al., 2004; Frederick et al., 1998). Thus, the HPA axis adapts to the stimulating effects of chronic smoking (see al'Absi, 2006 for review) and, during early abstinence, these changes result in an increase of activity that worsens withdrawal.

Heavy smokers also display disruptions in ANS system functioning. Like the HPA axis, acute nicotine administration increases heavy smokers' epinephrine, norepinephrine, blood pressure, and heart rate (DeVito et al., 2014; Foulds et al., 1997; Hill and Wynder, 1974; Mendelson et al., 2008; Minami et al., 1999; Sofuoglu et al., 2012, 2001; Tsuji et al., 1996; Wilkins et al., 1982). Acute administration of nicotine also increases LF HRV, decreases HF HRV, and increases the ratio of LF/HF HRV (Ashare et al., 2012; Barutcu et al., 2005; Karakaya et al., 2007; Kobayashi et al., 2005; Minami et al., 1999). Cigarette chippers have a more robust blood pressure response to nicotine than was noted in heavy smokers (Shiffman et al., 1992). Sustained abstinence appears to normalize ANS activity as evidenced by decreased epinephrine and norepinephrine levels and reduction in the LF/HF HRV (Minami et al., 1999). Nicotine, therefore, activates the peripheral ANS stress system in both acute response and overall tone that normalizes over sustained abstinence.

2.2. Cannabis

2.2.1. Acute effects of cannabis in light users

Δ1-tetrahydrocannabinol (THC) is the psychoactive component of cannabis. Administration of THC activates corticosterone/cortisol and ACTH in both animal (Kubena et al., 1971; Martí;n-Calderón et al., 1998; Puder et al., 1982) and human samples (D'Souza et al., 2004;

Hollister et al., 1970; Ranganathan et al., 2009). The action of exogenous cannabinoids on the HPA axis is complex, exerting both direct effects (Puder et al., 1982) on both the paraventricular nucleus of the hypothalamus and via other brain areas, including the basolateral amygdala (Armario, 2010). Acute smoked cannabis or oral THC stimulate cardiovascular arousal with increases observed in HR and plasma epinephrine (Hollister et al., 1970) and increases heart rate (Lindgren et al., 1981; Strougo et al., 2008; Zuurman et al., 2010).

2.2.2. Acute effects of cannabis in heavy users

Acute administration of smoked cannabis or oral THC in chronic users has also been shown to stimulate both the ANS and the HPA axis. With regard to the HPA axis, cortisol increases in response to either smoking marijuana or receiving intravenous THC has been reported (Cone et al., 1986; D'Souza et al., 2008; Ranganathan et al., 2009). However, the THC-induced rise in disordered users was blunted when it was compared to the cortisol increase in healthy controls (D'Souza et al., 2008; Ranganathan et al., 2009). Prolonged exposure to THC over the course of two weeks blunted the cortisol rise expected after administration (Benowitz et al., 1976). This previous finding combined with observed higher basal cortisol levels in heavy cannabis users (Cuttler et al., 2017; King et al., 2011) and sustained higher levels even after six months of abstinence (Somaini et al., 2012) suggest that continued cannabis use is associated with lasting adaptations in the HPA axis. It should be noted that based on these studies, it is unclear if chronic cannabis use alters stress function or vice versa. While some studies have found that THC does not impact epinephrine and norepinephrine concentration (Dumont et al., 2009), THC does induce a marked increase cardiovascular response in chronic users (Dumont et al., 2009; Haney et al., 2016; Lindgren et al., 1981; Ramesh et al., 2013; Vandrey et al., 2013), but this response does not differ between heavy and light cannabis smokers (Haney et al., 2016). Thus, acute exposure to the psychoactive components of cannabis increases HPA axis activity and cardiovascular arousal, but its effects on peripheral catecholamines are not clear and more research is needed. Abrupt cessation of smoking also caused blood pressure to increase dramatically (Vandrey et al., 2011); however, the abstinence-related increases in heart rate are delayed (Haney et al., 2018).

2.3. Stimulants

2.3.1. Acute effects of stimulants in naïve or light users

Cocaine increases corticosterone and cortisol in cocaine-naïve rodents (Borowsky and Kuhn, 1991; Levy et al., 1991; Moldow and Fischman, 1987; Saphier et al., 1993; Sarnyai et al., 1992) and humans (Heesch et al., 1995) in a dose-dependent fashion. Similarly, cocaine also increases ACTH in male rodents (Borowsky and Kuhn, 1991; Kuhn and Francis, 1997; Levy et al., 1991; Moldow and Fischman, 1987), although this was not replicated in the one human study (Heesch et al., 1995). Furthermore, it appears that CRF may play an important role in the mechanism of action of cocaine. One study found that CRF, when peripherally administered, blocks the effects of HPA response (Sarnyai et al., 1992). Gender may be an important moderator as indicated by one study that found female rats had a larger corticosterone response to cocaine than male (Kuhn and Francis, 1997). This finding is particularly important since most cocaine administration studies in naive populations have focused on male animals and humans. Cocaine also stimulates the ANS as evidenced by increased epinephrine and norepinephrine in an animal sample (Chiueh and Kopin, 1978) and increased heart rate in a human sample (Vongpatanasin et al., 2004). In human models, cocaine dramatically increases HR and reduces the activity of the parasympathetic nervous system as evidenced by reduced HF HRV (Vongpatanasin et al., 2004).

Another group of stimulants, amphetamines, has similar impacts on the HPA axis and adrenergic system. Similar to cocaine, amphetamines increase cortisol responding in human (de Wit et al., 2007; dos Santos et al., 2011; Halbreich et al., 1981; Jacobs et al., 1989; Nurnberger et al., 1984; L. M. Oswald et al., 2005; Sachar et al., 1980; Söderpalm et al., 2003; Wand et al., 2007; White et al., 2006) and rodent samples (Knych and Eisenberg, 1979; Swerdlow et al., 1993). Individuals with a history of using methamphetamine at least six times, but who were not dependent, had increased in cortisol in response to methamphetamine administration (Harris et al., 2006, 2003). CRF and other neurotransmitters mediate the cannabis-induced increase in cortisol (Armario, 2010; Swerdlow et al., 1993). In addition to its actions on the HPA axis, amphetamine also stimulates adrenergic response as evidenced by increased norepinephrine, blood pressure (Nurnberger et al., 1984), blood pressure (Nurnberger et al., 1984), and heart rate (de Wit et al., 2007). Amphetamine acutely activates the ANS of experienced, but not dependent, methamphetamine users as indexed by the norepinephrine metabolite, 3-methoxy-4-hydroxyphenylethylene glycol (MHPG) (Harris et al., 2006).

2.3.2. Acute and chronic effects of stimulants in dependent users

Several studies have demonstrated that cocaine increases corticosterone secretion (see Marinelli and Piazza, 2002 for review). In humans, chronic cocaine users also display higher cortisol and ACTH levels when administered cocaine (see Manetti et al., 2014 for review) and elevated basal levels of cortisol (Haney et al., 2001) that either are unchanged by abstinence (McDougle et al., 1994; Mendelson et al., 1988) or reduced with sustained abstinence from cocaine (Buydens-Branchey et al., 2002). Cocaine administration also increased the adrenergic response including catecholamine levels (Sofuoglu et al., 2001), blood pressure, and heart rate (Esel, 2001; see Foltin et al., 1995 for review; Kollins and Rush, 2002; Kosten et al., 1996; Lynch et al., 2008, 2006; Reid et al., 2006; Walsh et al., 2009) dose-dependently (Collins et al., 2007; Foltin et al., 2003; Lynch et al., 2006). Some studies have suggested that repeated exposure to cocaine sensitizes the heart rate response to cocaine with most robust responses occurring during laboratory-monitored cocaine binges (Kollins and Rush, 2002; Walsh et al., 2009, 2000). Other studies found that, after an initial rise in the subjective cardiovascular effects, the cardiovascular response flattens suggesting that individuals become tolerant to binge levels (Bitmead and Bitmead, 1984; Foltin et al., 2003; Ward et al., 1997). Reed and colleagues' (1984) dissection of the HR response by comparing the area-under-the-curve to the overall increases suggested that the increase in the cardiovascular response may be due to the conditioned response of pairing administration with contextual cues. During acute abstinence, the norepinephrine metabolite MHPG is increased as was systolic blood pressure in response to intranasal cocaine (McDougle et al., 1994). Basal cardiovascular levels are elevated in chronic cocaine users (Sharma et al., 2016).

The effects of amphetamines on cortisol levels in chronic users is complicated. Regular 3,4-methylenedioxymethamphetamine (MDMA or "ecstasy") users had higher hair cortisol levels than light, recent users or non-using controls (Parrott et al., 2014). One study found that amphetamine use while on placebo treatment was associated with a significantly lower cortisol level after administration relative to amphetamine-dependent individuals on naltrexone (Jayaram-Lindström et al., 2008); however, another study found that methamphetamine-increased cortisol and ACTH in experienced non-dependent users. The effect of amphetamines on basal levels of the HPA axis is not clear-cut. Some studies have found that non-treatment seeking chronic methamphetamine users had lower (Carson et al., 2012) or no differences in basal cortisol levels (Zorick et al., 2011) as compared to controls subjects. The latter correlational study found no differences between individuals with methamphetamine dependence and control subjects after four weeks of abstinence. Methamphetamine-dependent individuals had altered sympathetic tone with increased LF HRV, decreased HF HRV, and higher LF/HF ratio, and greater use positively correlated with the latter (Henry et al., 2012). More research is necessary to understand the effects that amphetamines have in stimulant-dependent individuals fully.

2.4. Alcohol

2.4.1. Acute effects of alcohol in light drinkers/naïve individuals

Alcohol acutely stimulates the HPA axis in non-dependent users. In rats, alcohol has been shown to consistently increase plasma corticosterone and ACTH levels (Allen et al., 2011; Richardson et al., 2008). In humans, similar increases in cortisol have been noted in response to acute alcohol administration (Frias et al., 2000; Gianoulakis et al., 1996; Mendelson and Stein, 1966; Välimäki et al., 1984; W.J. et al., 1995). It appears the effects of alcohol on the HPA axis occurs primarily due to alcohol's actions on the paraventricular nucleus of the hypothalamus (Armario, 2010). With respect to ANS activation, animal models have demonstrated elevated epinephrine and norepinephrine response to intravenous alcohol administration (Livezey et al., 1987; Perman, 1960) and, similar to the observations with the HPA axis in humans, found that alcohol blunted the expected stress response when the animals were confronted with a stressor. In humans, noradrenaline responses were also elevated and peaked about 30 min after drinking 0.9 g/kg of alcohol and remained high after 4 h (Howes and Reid, 1985). Acute alcohol administration also appears to impact cardiovascular indices of increased sympathetic arousal. Acute alcohol administration in moderate to high doses consistently decreases high-frequency HRV and also increases the ratio of low frequency to high-frequency heart rate variability, an index of sympathetic to parasympathetic function (Romanowicz et al., 2011). Collectively, these results are consistent with animal studies and suggest that alcohol acutely increases HPA axis and ANS activity in naive alcohol users and may further blunt the stress response when administered in close temporal proximity to a stressor.

2.4.2. Acute effects of alcohol in binge and alcohol-dependent samples

Persistent binge drinking alters the HPA axis and ANS system via the repeated activation by frequent, heavy alcohol use. Basal cortisol levels are elevated in binge heavy men (Blaine et al., 2018; Thayer et al., 2006) and women (Wemm et al., 2013). Furthermore, the expected rise in cortisol in response to alcohol administration was blunted in heavy relative to light/moderate social drinkers (King et al., 2006). Basal HRV levels appear to significantly lower in heavy drinking males, indicating decreased functioning of the ANS (Thayer et al., 2006). Also, individuals who were heavy drinkers five years prior had a reduced cortisol response to alcohol relative to those who were light drinkers (King et al., 2016).

Alcohol stimulates cortisol levels in both dependent animals (Richardson et al., 2008) and humans (Adinoff et al., 2003; Feller et al., 2014; Mendelson and Stein, 1966; Stokes, 1973). When an individual abstains from alcohol, withdrawal is also associated with increased basal cortisol levels (Mendelson and Stein, 1966) and decreased diurnal variation (Adinoff et al., 1991; Risher-Flowers et al., 1988). Cortisol tone also tends to be increased during periods of heavy drinking (Wand and Dobs, 1991). Although basal cortisol levels decrease during longer abstinence (Motaghinejad et al., 2015), sustained abstinence is associated with increased basal cortisol levels as compared to healthy controls (Starcke et al., 2013). Activation of the ANS system in alcohol-dependent individuals is also affected by alcohol. Acute intoxication was associated with increases in MHPG (Borg et al., 1981) and, as dependent individuals enter acute withdrawal, levels of MHPG decrease as time since their last drink increase (Hawley et al., 1994). Although not tested directly in response to acute intoxication, adaptive HRV functioning is also directly modified by alcohol dependence. A meta-analysis found that alcohol dependence, regardless of treatment setting, is associated with a decrease in basal HF HRV levels (Quintana et al., 2013). Collectively, the results from these studies point to neuroadaptations in HPA and ANS response with active binge and chronic use such that there is a blunted or lack of a phasic response but elevated tonic levels in binge/disordered users relative to controls.

2.5. Opioids

2.5.1. Acute effects of opioids in non- and light users

Unlike other drugs of abuse, opioids appear to have different effects on stress biology in rodent as compared to humans. In rats, morphine increases ACTH and corticosterone (Buckingham and Cooper, 1986; Eisenberg, 1985; Suemaru et al., 1989) whereas, in humans, morphine dampens the HPA response (Delitala et al., 1983; George et al., 1974; Rittmaster et al., 1985; Zis et al., 1984). Naloxone, an opioid antagonist, increases ACTH and cortisol levels in humans (Grossman et al., 1986; Naber et al., 1981) and pigs (Richard et al., 1986; Rushen et al., 1993). There is evidence that opioids directly impact the HPA axis (Vuong et al., 2010) to suppress HPA axis responses. The impact of opioids on the ANS is complex, with decreasing response of HPA axis to CRF, morphine had limited impact on the epinephrine and norepinephrine response (Rittmaster et al., 1985). Although opioids decrease heart rate and blood pressure (Suemaru et al., 1989), high-frequency HRV has been shown to be decreased by opioids (Latson et al., 1992).

2.5.2. Chronic effects of opioids on stress systems in dependent samples

In human samples, opioids and opioid agonists, including methadone and buprenorphine, acutely suppress cortisol levels (Cami et al., 1992; Mendelson et al., 1975; Nava et al., 2006; Walter et al., 2011, 2008) and basal cortisol levels tend to be higher in opioid-dependent users as compared to healthy controls (Walter et al., 2011). One early study found that cortisol was unchanged by heroin administration (Mendelson et al., 1975); and a more recent study found that diacetylmorphine, the pharmaceutical version of heroin prescribed for maintenance therapy, decreased cortisol levels more so than methadone (Walter et al., 2011). Withdrawal from opioids corresponds with significant tonic increases in ACTH and cortisol levels regardless of whether it was induced by a naloxone challenge (Gerra et al., 2003) or occurred naturally over time (Shi et al., 2009). Acute administration of intravenous opioids is associated with an initial spike in heart rate that is followed by a delayed reduction in heart rate (Kennedy et al., 2015; Rook et al., 2006). A similar pattern of results was found for withdrawal-related effects on the SAM system. Specifically, epinephrine, norepinephrine, LF HRV, and blood pressure increase in response to naloxone-induced withdrawal (Hoffman et al., 1998; Kienbaum et al., 1998; McDonald et al., 1999).

On the basis of the review presented in the previous sections, Table 1 summarizes the direction of phasic HPA axis and ANS responses

Table 1
Acute drug response in non-disordered/lightly using subjects and actively using binge/disordered substance users.

Substance	Acute Drug Response		**Binge/Disordered vs.** Naïve/Non-Disordered*	
	HPA	ANS	HPA	ANS
Nicotine	↑	↑	↓	↓
Cocaine	↑	↑	?	?
Amphetamine	↑ ↓	↑	?	?
Cannabis	↑	↑	↓	↑
Alcohol	↑	↑	↓	↑
Opioids	↓	↑	?	?

Note: In autonomic nervous system activity, LF HRV is indicative of an activated sympathetic nervous system response, whereas HF HRV is reflective of parasympathetic response. Here, we focused on activation of the sympathetic nervous system within the autonomic nervous system.
* Acute phasic effects of drugs on the HPA axis and the ANS in non-disordered/lightly using (non-weekly use at very low levels) subjects as compared to actively using binge/disordered users.
↑ indicates activation; ↓ indicates reduction; ↑ ↓ indicates mixed results; = indicates similar responses; ? indicates areas for future research.

to acute administration of each psychoactive drug of abuse in naïve/non-disordered and adaptations in these responses with binge/heavy and dependent users relative to controls.

3. Drug-related adaptations in stress biology, reward, craving and relapse risk

The previous sections and Table 1 highlights the potent effects of the most common psychoactive drugs on stress biology with acute effects of stimulation for nicotine, cannabis, stimulant, and alcohol, and depressive effects of acute opioids in humans. More importantly, regular, binge and chronic use of drugs alter these stress responses, signaling significant adaptations in stress biology. As substance use escalates in frequency and intensity, adaptations in HPA axis and ANS pathways manifest as changes in basal levels, but also in phasic responses to drug, stress and challenge (see al'Absi, 2006 for review of nicotine; Ashare et al., 2012; see Blaine and Sinha, 2017 for review of alcohol; McKee et al., 2011; McRae-Clark et al., 2011). In turn, withdrawal-related basal increases in cortisol are associated with cognitive impairments (Errico et al., 2002). In turn, these cognitive impairments could perpetuate the worsening of addiction (see Bernardin et al., 2014; Besson and Forget, 2016; Spronk et al., 2013 for discussion).

This cumulative evidence begs the question of whether such adaptations in stress biology are the mere consequences of drug use, or if they also serve as interoceptive drug-related adaptations that may play a role in motivating compulsive drug use and relapse risk in chronic users. There have been decades of focus on mesolimbic striatal dopaminergic pathways as critical for the reinforcing effects of psychoactive drugs. While striatal adaptation may drive compulsive drug motivation, other positron emission tomography (PET) evidence indicates that psychoactive drug-stimulated increases in cortisol is highly correlated with dopamine release in the striatum (Booij et al., 2016; Cox et al., 2009; Wand et al., 2007) and drug-induced cortisol increases are associated with the subjective intoxication in healthy volunteers (Oswald et al., 2005). Similarly, psychological stress provocation in healthy volunteers has also been shown to increase dopamine transmission in the striatum and the PFC (Nagano-Saito et al., 2013; Pruessner et al., 2004), and cortisol responses to psychosocial stressors predict reward after amphetamine administration (Hamidovic et al., 2010). In a functional magnetic resonance imaging (fMRI), a psychological stress provocation results in robust striatal activation, specifically in the ventral striatum but not the dorsal striatum relative to non-stress cues in healthy volunteers (Sinha et al., 2016). Also, activity in the ventromedial prefrontal cortex and the rostral anterior cingulate cortex was predictive of resilient coping and low levels of alcohol use. Consistent with these findings, other fMRI studies have shown blunted stress responses in at-risk individuals is predictive of blunted central brain activity in limbic-striatal and prefrontal regions (Carroll et al., 2017; Ginty, 2013) that are critical for regulating motivated behavior and resilient coping. Other PET research has reported a loss of dopamine transmission and blunted dopamine release in drug-abusing patients is correlated with severity of addiction as well as with increases in compulsive motivation for drug and treatment failure (Martinez et al., 2011; Martinez and Narendran, 2010). Whether these blunted dopamine changes are related to blunted glucocorticoid responses to drug or stress has not been fully investigated. Nonetheless, these data highlight that drug-induced activation of stress and dopaminergic pathways are highly interactive and suggest that both may jointly play a role in psychoactive drug effects, and on compulsive drug motivation.

Findings from several well-controlled laboratory studies in treatment-seeking or non-treatment seeking and acutely abstinent drug-abusing patients have shown a blunted stress cortisol and ANS axis response to stress and drug cue provocations along with higher basal cortisol and HR along with disrupted HRV responses (Table 2; see Sinha, 2008 and Milivojevic and Sinha, 2018 for review). Such responses are predictive of higher relapse risk after treatment and co-occur with greater drug craving during stress and drug cue provocation (Ashare et al., 2012; McKee et al., 2011; Milivojevic and Sinha, 2018; Sinha, 2011; Sinha et al., 2006). Blunted cortisol arousal to stress cues is also predictive of increased alcohol motivation to drink alcohol in binge, heavy drinkers (Blaine et al., 2018). Thus, these studies consistently link adaptations and changes in peripheral and central stress responses to compulsive drug motivation and relapse risk, thereby suggesting a need to target these pathways as both markers of addiction risk and severity but also in treatment development (Milivojevic and Sinha, 2018).

Table 2
Basal states and stress- and drug-cue induced responses in substance abusing compared to healthy control subjects.

Substance	Tonic/Basal State		Stress Provocation		Drug Cues	
	HPA	ANS	HPA	ANS	HPA	ANS
Nicotine	↑	↑	↓	↑ =	?	↑
Cannabis	↑	↑	↓	?	↓	↑
Cocaine	↑	↑	↓	↑ =	↑ =	↑ =
Amphetamine	↑ ↓ =	↑	↓	=	?	?
Alcohol	↑	↑	↓	↓ =	?	↑
Opioids	↑	↑	↑ ↓	↓	↑ ?	↑

Note: A comparison of the tonic levels and acute/phasic effects of stress and drug cues exposure on the HPA axis and the ANS in non-disordered healthy controls chronic, binge/substance abusing individuals (not in acute abstinence or withdrawal). In autonomic nervous system activity, LF HRV is indicative of an activated sympathetic nervous system response, whereas HF HRV is reflective of parasympathetic response. Here, we focused on activation of the sympathetic nervous system within the autonomic nervous system.
↑ indicates activation; ↓ indicates reduction; ↑ ↓ indicates mixed results; = indicates similar responses; ↑ ? = limited evidence, needs more research; ? indicates areas for future research.

On the basis of the review presented in previous sections, we present a heuristic model to illustrate the drug-stress motivation cycle in Fig. 2. The findings presented earlier suggest a *feed-forward* cascade of effects of drugs on stress biology. Our stress biology is wired to help us to adapt to life's struggles but, in the face of increasing drug use and abuse, this critical biological process is handicapped and blunted. Consequently, heavy and chronic drug users are more vulnerable to negative affect, distress and poor stress coping. Furthermore, with blunted or more "tolerant" stress responses to drug use, greater levels of drug use are needed to maintain allostasis, thereby driving a cycle of increased drug use and stress disruption that further drive greater compulsive drug motivation and relapse risk.

4. Factors affecting drug effects on stress responses

4.1. Effects of drugs on responding to a stressor

We focused specifically on the effect of drugs on the activity of the HPA axis and the SAM system in the previous sections; however, anecdotal evidence from patients and several theories of substance use point to the fact that a stressor often precedes use, thus likely modifying the response to the stressor. In an experimental model of this observation, studies have shown that the simultaneous administration of a drug with a stressor disrupts the normal stress response system (Van Hedger et al., 2017). For example, when alcohol or methamphetamine is administered following a stressor, the drug impairs the cortisol response to psychosocial and pharmacological stressors (Childs et al., 2010; Söderpalm et al., 2003). Alcohol administered immediately after a stressor prolonged the negative affect and increased craving in response to the stressor (Childs et al., 2011). When low doses of THC was administered after a stressor, the subjective distress was also blunted; however, at high doses of THC, negative affect was increased, and blood pressure was blunted (Childs et al., 2017). In a human laboratory model

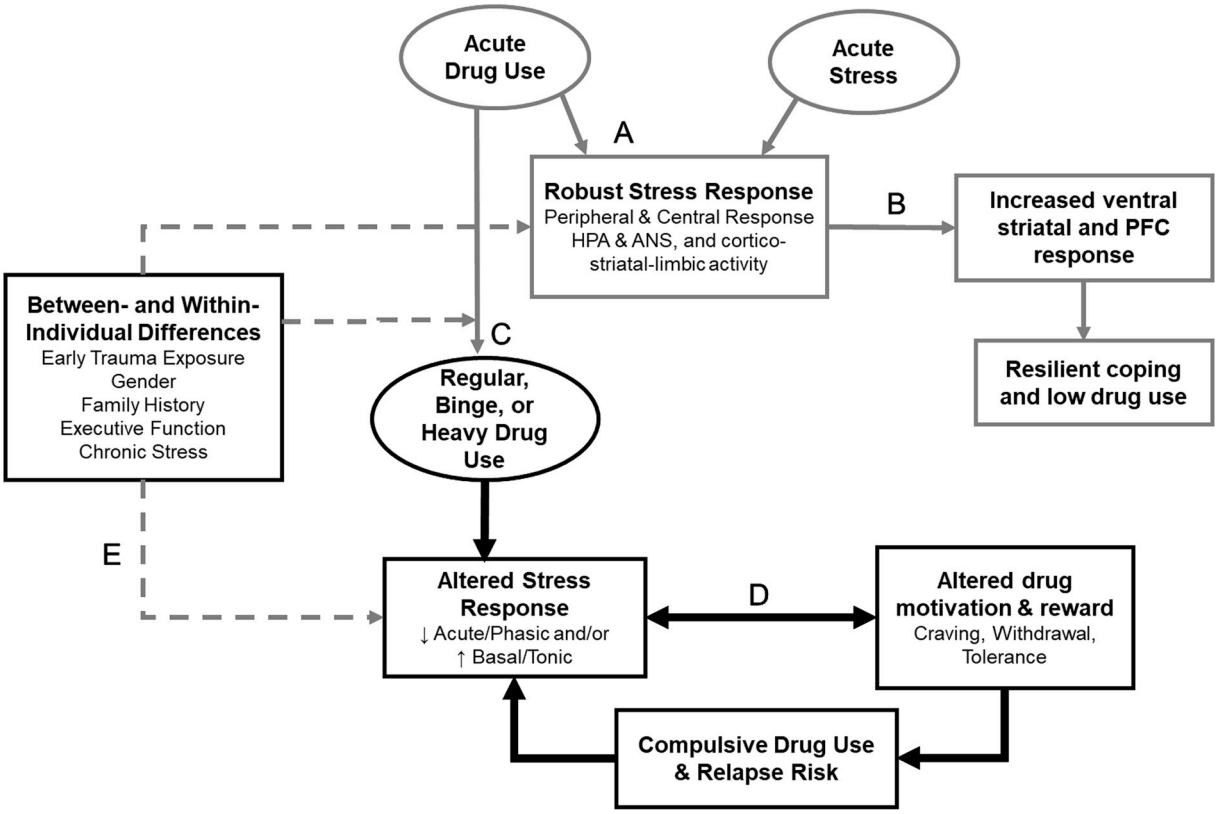

Fig. 2. A heuristic framework for drug-induced stress and reward interactions is presented to illustrate the effects and acute and chronic drug intake on the stress biology and their effects on drug motivation and compulsive drug use. **A** refers to the effects of acute drug use or stress on peripheral and central stress response in light or inexperienced drug users. **B** describes the central striatal-prefrontal effects in these healthy individuals that encode drug learning, neuroflexibility, and resilient coping that results in controlled, low levels of drug intake in light drug users with robust stress responses. **C** indicates the mediating process of increased binge and heavy use that results in an altered and blunted stress and reward response in vulnerable individuals. **D** shows the blunted response then results in the feed-forward cascade of increased craving, neuroendocrine tolerance, and acute abstinence/withdrawal effects that play a role in compulsive drug use and relapse risk. **E** highlights potential moderators that make individuals more vulnerable or more resilient in each of the previous processes.

of smoking relapse, exposure to a stressor increased the rewarding effects of smoking, which was correlated to cortisol (McKee et al., 2011). However, these effects may depend on the type of drug administered. In opioids, cortisol administration was found to reduce craving in patients with low-dose heroin consumption (Walter et al., 2015). This finding is perhaps not surprising given that opioids have a dampening effect on the HPA axis system whereas the other substances of abuse have an activating effect. Further research is necessary to fully understand the interactive impact of a drug and stress on stress system responsivity.

4.2. Drug-related factors influencing stress responses

A host of methodological factors (e.g., frequency and amount of recent drug use, rapidity and amount of acute drug intake, the dose of the drug administered and tested, type of drug within a broad drug class, route of administration) could potentially impact the strength of the drug effects on the stress responses. Notably, Allain et al. (2015) discuss the role of frequency of drug use and rapidity of use during bouts as significant aspects of compulsive drug seeking and addiction risk. Self-motivational aspects of how often drug is used and the use topography may influence both subjective drug effects, drug-related stress responses, and drug motivation for continued drug use.

In other research, King and colleagues found that high dose alcohol (0.8 g/kg) increased cortisol levels in light drinkers whereas a low dose of alcohol (0.4 g/kg) did not and that heavy binge drinkers showed blunted cortisol responses (King et al., 2006). On the other hand, Blaine et al. (2018) showed low levels of alcoholic beer consumed under a behavioral motivation paradigm increased cortisol in both moderate non-binge and binge-heavy users. The articles reviewed here use a variety of administration methods, including intravenous, intranasal, oral, and self-administration. Each route has differences in the rate of absorption which would have different impacts on the reactivity of the stress systems (Gourlay and Benowitz, 1997). Another important methodological consideration is the impact of recent drug use history on the acute drug responses. For example, Ramchandani et al. (2002) found that increased drinking in the past month before participating in the study predicted the acute subjective and psychomotor response after an intravenous alcohol administration. Most studies that have investigated the effect of drugs on the stress systems have required that individuals remain abstinent for a certain period prior to participating in the study; however, some individuals may choose to begin abstinence in advance of their participation and, thus, may have differential responses to drug administration depending on their length of abstinence. Relatedly, given the impact of withdrawal on the HPA axis, it is also likely that the stress system response to drug administration may also vary depending on their stage of withdrawal.

4.3. Factors that influence the response to stress

Family History: Other studies suggest that participant factors, such as a family history of alcohol use disorder, may also play a role. Non-dependent participants with a family history of alcohol use disorders have consistently displayed an alcohol-induced reduction in cortisol and ACTH relative to individuals without such a family history (Schuckit et al., 1996; Zimmermann et al., 2004). Collectively, findings from these studies suggest that individuals who may be genetically

predisposed already show patterns of reactivity like dependent users.

Co-Occurring Drug Use: Most of the research studies discussed in this article focused on samples that were dependent on a single drug; however, most individuals who seek treatment for substance use disorders report abusing several different types of drug or have a history of dependence on other substances. Individuals with marijuana use experience greater reinforcing effects of nicotine use (Perkins et al., 2009). Combined administration of cocaine and marijuana results in an increased cardiovascular response and poor cognitive performance as compared to the effect of either drug alone (Foltin et al., 1995, 1993; 1987; Foltin and Fischman, 1990). Other studies have found that combined use of cannabis with MDMA results in an enhanced acute subjective and stress system response to the drugs (Dumont et al., 2009; Kollins et al., 2015). Findings from our laboratory indicate that a history of marijuana dependence with alcohol or cocaine use dysregulates HPA axis responding to stress- and drug-related cues (Fox et al., 2013). Nicotine increases the self-administration alcohol (Barrett et al., 2006) and, at low doses of nicotine, increases the alcohol-induced dopamine release in the VTA (Tizabi et al., 2002). Despite this, we know little about the impact of polysubstance disorders or other past drug history has on the HPA axis and ANS response to drugs.

Gender: Drug response may also differ by gender. Women, overall, tend to report greater sensitivity to drug effects as compared to men. For example, women tend to show greater sensitivity to the negative effects of intravenous nicotine administration as compared to men (DeVito et al., 2014; Sofuoglu and Mooney, 2009), and men tend to show greater initial reward sensitivity intranasal administration of nicotine (Perkins et al., 2009). In response to cocaine, women reported greater anxiety following administration (Kosten et al., 1996) and reduced high (Lynch et al., 2008) as compared to men. Men tend to have higher amphetamine-induced dopamine release in striatal regions and report correspondingly more rewarding effects of the drug as compared to women (Munro et al., 2006). The effects of these drugs in women may also vary across the menstrual cycle. Alcohol metabolism differs across the menstrual cycle, such that faster rates of elimination are noted in the mid-luteal phase as compared to the early follicular and ovulatory phases (Sutker et al., 1987). Women in the luteal phase of their cycle showed decreased responses to cocaine (Sofuoglu et al., 1999), nicotine (DeVito et al., 2014), and amphetamine (Justice and de Wit, 1999) as compared to those in their follicular cycle. Although one study found limited effects of sex and menstrual cycle on the response to intranasal cocaine (Collins et al., 2007). These collective results suggest that neuroactive steroids, such as estrogen and progesterone, play an important role in the metabolism and effects of drug administration.

Developmental Stage and Early Trauma: There is evidence that blunted stress reactivity is a predictor of earlier use of substances (Evans et al., 2012; Huizink et al., 2006), and that individuals with a blunted cortisol response to stress are at increased risk for substance use (Lovallo, 2006). However, it is unclear if this blunted responding becomes exacerbated by exposure to drugs and at what developmental periods are at-risk individuals most vulnerable. Exposure to early life adversity has known impacts on the HPA axis (Lovallo, 2013) and increases the likelihood that these individuals will develop addictive disorders later in life (Doan et al., 2014; see Enoch, 2011 for review; Gerra et al., 2014). Early life adversity is positively associated with dopamine response to amphetamine in the ventral striatum (Oswald et al., 2014) and lower gray matter volume in limbic regions in individuals in treatment for substance use disorders and also predicted a shorter time to relapse, regardless of type of drug (Van Dam et al., 2014). In cocaine-dependent individuals, early life adversity increased the cortisol response to stress although there was no healthy control to determine if this response was blunted (Flanagan et al., 2015). A recent study found that early life adversity moderated the impact of withdrawal on stress system response to a stressor (al'Absi et al., 2018). However, few studies have tested these associations systematically in response to stress, and even fewer still have assessed the impact of early life adversity in response to administration of drugs.

5. Conclusions and future directions

Intake of psychoactive drugs has significant acute effects on the peripheral stress pathways. These effects parallel drug-related effects on central stress and reward pathways to alter acute drug-related subjective, neuroendocrine, and physiological states. Regular, high levels of drug use alter stress and reward responses both in tonic and phasic responding and recent findings suggest that such alterations are significantly associated with the tolerance, withdrawal and intoxication effects of drugs as well as in predicting current drug use and future relapse. This review suggests that addictive substances, although varying in neurobiological targets of action, are similar in having a significant and potent effect on stress pathways, to affect stress responses, craving, and drug intake.

However, it should be noted that there are limits to what can be concluded from the current literature and important areas for future research. Most studies discussed here have focused entirely on either naïve participants/light users or chronic/dependent users; only a few have compared across different types of users. For those that have compared across substances, chronic use is generally associated with a blunting of the drug-induced activation of the stress systems (Holdstock et al., 2000; King et al., 2006; Stormark et al., 1998; Thayer et al., 2006); however, this has not been fully elucidated in many drugs. More research comparing light users to heavy users is necessary to understand the neuroadaptations that occur to drug administration fully. Additionally, most studies compare stress reactivity in chronic substance users to healthy controls are cross-sectional. Thus, it cannot be determined if the stress dysregulation of heavy users is caused by chronic exposure to substances or predisposes them to future drug use. It is probably, and indeed very likely, that the effect is synergistic. Individuals with a disrupted stress response, due to early trauma or family history, are more likely to abuse drugs, which in turn further dysregulates their stress response. Thus, longitudinal research, such as the massive undertaking that is the Adolescent Brain Cognitive Development (ABCD) study, is vital for determining if drug use results in adaptations to the stress response system or exacerbates pre-existing stress dysregulation. Chaplin and colleagues in this special issue address these temporal associations in an excellent overview of the developmental aspects of the link between substance use and stress response dysregulation.

Substance-related adaptations to the stress system may occur along a continuum. By artificially focusing on one end of the spectrum or the other, we may not be capturing the full spectrum of neuroadaptations in the stress response to addictive substances. Animal models to some extent can address this continuum but, such as seen in opiates (Armario, 2010), the stress system response to drug intake may differ between animals and humans. A future review should synthesize findings across species. Finally, certain individual differences, some of which have been noted above, may hasten or slow down the progression along this continuum.

Despite the gaps in the literature, these findings collectively suggest that dysregulation of the stress responses may serve as potential markers for prevention efforts and a target for the development of therapeutic interventions (Greenwald, 2018; Milivojevic and Sinha, 2018). Prevention efforts that target individuals with certain risk factors known to impact the stress system (e.g., early life adversity, genetic, family history) may reduce the likelihood that these individuals will develop a substance use disorder. Concerning treatment efforts for individuals with addictive disorders, the extant treatments are modestly effective at best. There is preliminary evidence that pharmacological interventions that target the adrenergic system may reduce craving evoked by both drugs and stress (Fox and Sinha, 2014; Fox et al., 2012; Lê et al., 2011; Milivojevic and Sinha, 2018). Behavioral treatments

that address the management of stress-related craving could enhance the efficacy of existing treatments. Thus, identifying specific biomarkers related to dysregulated stress responses might allow us to identify novel treatment approaches targeting normalizing of the stress response to improve addiction treatment efforts.

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References

Acri, J.B., 1994. Nicotine modulates effects of stress on acoustic startle reflexes in rats: dependence on dose, stressor and initial reactivity. Psychopharmacology (Berl) 116, 255–265. https://doi.org/10.1007/BF02245326.

Adinoff, B., Risher-Flowers, D., De Jong, J., Ravitz, B., Bone, G.H.A., Nutt, D.J., Roehrich, L., Martin, P.R., Linnoila, M., 1991. Disturbances of hypothalamic-pituitary-adrenal axis functioning during ethanol withdrawal in six men. Am. J. Psychiatry 148, 1023–1025. https://doi.org/10.1176/ajp.148.8.1023.

Adinoff, B., Ruether, K., Krebaum, S., Iranmanesh, A., Williams, M.J., 2003. Increased salivary cortisol concentrations during chronic alcohol intoxication in a naturalistic clinical sample of men. Alcohol Clin. Exp. Res. 27, 1420–1427. https://doi.org/10.1097/01.ALC.0000087581.13912.64.

al'Absi, M., 2006. Hypothalamic-Pituitary-Adrenocortical responses to psychological stress and risk for smoking relapse. Int. J. Psychophysiol. 59, 218–227. https://doi.org/https://doi.org/10.1016/j.ijpsycho.2005.10.010.

al'Absi, M., Nakajima, M., Lemieux, A., 2018. Impact of early life adversity on the stress biobehavioral response during nicotine withdrawal. Psychoneuroendocrinology 98, 108–118. https://doi.org/10.1016/J.PSYNEUEN.2018.08.022.

Allen, C.D., Rivier, C.L., Lee, S.Y., 2011. Adolescent alcohol exposure alters the central brain circuits known to regulate the stress response. Neuroscience 182, 162–168. https://doi.org/10.1016/J.NEUROSCIENCE.2011.03.003.

Armario, A., 2010. Activation of the hypothalamic-pituitary-adrenal axis by addictive drugs: Different pathways, common outcome. Trends Pharmacol. Sci. https://doi.org/10.1016/j.tips.2010.04.005.

Ashare, R.L., Sinha, R., Lampert, R., Weinberger, A.H., Anderson, G.M., Lavery, M.E., Yanagisawa, K., McKee, S.A., 2012. Blunted vagal reactivity predicts stress-precipitated tobacco smoking. Psychopharmacology (Berl) 220, 259–268. https://doi.org/10.1007/s00213-011-2473-3.

Barrett, S.P., Tichauer, M., Leyton, M., Pihl, R.O., 2006. Nicotine increases alcohol self-administration in non-dependent male smokers. Drug Alcohol Depend. 81, 197–204. https://doi.org/10.1016/J.DRUGALCDEP.2005.06.009.

Barutcu, I., Esen, A.M., Kaya, D., Turkmen, M., Karakaya, O., Melek, M., Esen, O.B., Basaran, Y., 2005. Cigarette Smoking and Heart Rate Variability: Dynamic Influence of Parasympathetic and Sympathetic Maneuvers. Ann. Noninvasive Electrocardiol. 10, 324–329. https://doi.org/10.1111/j.1542-474X.2005.00636.x.

Benowitz, N.L., Jones, R.T., Lerner, C.B., 1976. Depression of Growth Hormone and Cortisol Response to Insulin-Induced Hypoglycemia After Prolonged Oral Delta-9-Tetrahydrocannabinol Administration in Man. J. Clin. Endocrinol. Metab. 42, 938–941.

Bernardin, F., Maheut-Bosser, A., Paille, F., 2014. Cognitive impairments in alcohol-dependent subjects. Front. Psychiatry. https://doi.org/10.3389/fpsyt.2014.00078.

Besson, M., Forget, B., 2016. Cognitive Dysfunction, Affective States, and Vulnerability to Nicotine Addiction: A Multifactorial Perspective. Front. Psychiatry 7, 160. https://doi.org/10.3389/fpsyt.2016.00160.

Bitmead, R.R., Bitmead, R.R., 1984. Convergence Properties of LMS Adaptive Estimators with Unbounded Dependent Inputs. IEEE Trans. Automat. Contr. 29, 477–479. https://doi.org/10.1016/j.drugalcdep.2009.02.004.

Blaine, S.K., Sinha, R., 2017. Alcohol, stress, and glucocorticoids: From risk to dependence and relapse in alcohol use disorders. Neuropharmacology 122, 136–147. https://doi.org/10.1016/j.neuropharm.2017.01.037.

Blaine, S.K., Nautiyal, N., Hart, R., Guarnaccia, J.B., Sinha, R., 2018. Craving, cortisol and behavioral alcohol motivation responses to stress and alcohol cue contexts and discrete cues in binge and non-binge drinkers. Addict. Biol. https://doi.org/10.1111/adb.12665.

Booij, L., Welfeld, K., Leyton, M., Dagher, A., Boileau, I., Sibon, I., Baker, G.B., Diksic, M., Soucy, J.P., Pruessner, J.C., Cawley-Fiset, E., Casey, K.F., Benkelfat, C., 2016. Dopamine cross-sensitization between psychostimulant drugs and stress in healthy male volunteers. Transl. Psychiatry 6 e740. https://doi.org/10.1038/tp.2016.6.

Borg, S., Kvande, H., Sedvall, G., 1981. Central norepinephrine metabolism during alcohol intoxication in addicts and healthy volunteers. Science 213, 1135–1137. https://doi.org/10.1126/SCIENCE.7268421.

Borowsky, B., Kuhn, C.M., 1991. Monoamine mediation of cocaine-induced hypothalamo-pituitary-adrenal activation. J. Pharmacol. Exp. Therapeut. 256, 204–210.

Brady, J.E., Li, G., 2014. Trends in alcohol and other drugs detected in fatally injured drivers in the United States, 1999-2010. Am. J. Epidemiol. 179, 692–699. https://doi.org/10.1093/aje/kwt327.

Buckingham, J., Cooper, T.A., 1986. Effects of Naloxone on Hypothalamo-Pituitary-Adrenocortical Activity in the Rat. Neuroendocrinology 42, 421–426.

Buydens-Branchey, L., Branchey, M., Hudson, J., Dorota Majewska, M., 2002. Perturbations of plasma cortisol and DHEA-S following discontinuation of cocaine use in cocaine addicts. Psychoneuroendocrinology 27, 83–97.

Cami, J., Gilabert, M., San, L., De La Torre, R., 1992. Hypercortisolism after opioid discontinuation in rapid detoxification of heroin addicts. Br. J. Addict. 87, 1145–1151. https://doi.org/10.1111/j.1360-0443.1992.tb02001.x.

Carroll, D., Ginty, A.T., Whittaker, A.C., Lovallo, W.R., de Rooij, S.R., Rooij, de, 2017. Title: The behavioural, cognitive, and neural corollaries of blunted cardiovascular and cortisol reactions to acute psychological stress. Neurosci. Biobehav. Rev. https://doi.org/10.1016/j.neubiorev.2017.02.025.

Carson, D.S., Bosanquet, D.P., Carter, C.S., Pournajafi-Nazarloo, H., Blaszczynski, A., McGregor, I.S., 2012. Preliminary evidence for lowered basal cortisol in a naturalistic sample of methamphetamine polydrug users. Exp. Clin. Psychopharmacol 20, 497–503. https://doi.org/10.1037/a0029976.

Chen, H., Fu, Y., Sharp, B.M., 2008. Chronic nicotine self-administration augments hypothalamic–pituitary–adrenal responses to mild acute stress. Neuropsychopharmacology 33, 721–730. https://doi.org/https://doi.org/10.1038/sj.npp.1301466.

Childs, E., Dlugos, A., De Wit, H., 2010. Cardiovascular, hormonal, and emotional responses to the TSST in relation to sex and menstrual cycle phase. Psychophysiology 47, 550–559. https://doi.org/10.1111/j.1469-8986.2009.00961.x.

Childs, E., O'Connor, S., de Wit, H., 2011. Bidirectional interactions between acute psychosocial stress and acute intravenous alcohol in healthy men. Alcohol Clin. Exp. Res. 35, 1794–1803. https://doi.org/https://doi.org/10.1111/j.1530-0277.2011.01522.x.

Childs, E., Lutz, J.A., de Wit, H., 2017. Dose-related effects of delta-9-THC on emotional responses to acute psychosocial stress. Drug Alcohol Depend. 177, 136–144. https://doi.org/10.1016/J.DRUGALCDEP.2017.03.030.

Chiueh, C.C., Kopin, I.J., 1978. Centrally mediated release by cocaine of endogenous epinephrine and norepinephrine from the sympathoadrenal medullary system of unanesthetized rats. J. Pharmacol. Exp. Therapeut. 205, 148–154.

Cohen, L.M., al'Absi, M., Collins Jr., F.L., 2004. Salivary cortisol concentrations are associated with acute nicotine withdrawal. Addict. Behav. 29, 1673–1678. https://doi.org/https://doi.org/10.1016/j.addbeh.2004.02.059.

Collins, S.L., Evans, S.M., Foltin, R.W., Haney, M., 2007. Intranasal cocaine in humans: Effects of sex and menstrual cycle. Pharmacol. Biochem. Behav. 86, 117–124. https://doi.org/10.1016/j.pbb.2006.12.015.

Cone, E.J., Johnson, R.E., Moore, J.D., Roache, J.D., 1986. Acute effects of smoking marijuana on hormones, subjective effects and performance in male human subjects. Pharmacol. Biochem. Behav. 24, 1749–1754. https://doi.org/10.1016/0091-3057(86)90515-0.

Cox, S.M.L., Benkelfat, C., Dagher, A., Delaney, J.S., Durand, F., McKenzie, S.A., Kolivakis, T., Casey, K.F., Leyton, M., 2009. Striatal Dopamine Responses to Intranasal Cocaine Self-Administration in Humans. Biol. Psychiatry 65, 846–850. https://doi.org/10.1016/j.biopsych.2009.01.021.

Cuttler, C., Spradlin, A., Nusbaum, A.T., Whitney, P., Hinson, J.M., McLaughlin, R.J., 2017. Blunted stress reactivity in chronic cannabis users. Psychopharmacology (Berl) 234, 2299–2309. https://doi.org/10.1007/s00213-017-4648-z.

D'Souza, D.C., Perry, E., MacDougall, L., Ammerman, Y., Cooper, T., Wu, Y., Braley, G., Gueorguieva, R., Krystal, J.H., 2004. The Psychotomimetic Effects of Intravenous Delta-9-Tetrahydrocannabinol in Healthy Individuals: Implications for Psychosis. Neuropsychopharmacology 29, 1558–1572. https://doi.org/10.1038/sj.npp.1300496.

D'Souza, D.C., Ranganathan, M., Braley, G., Gueorguieva, R., Zimolo, Z., Cooper, T., Perry, E., Krystal, J., 2008. Blunted Psychotomimetic and Amnestic Effects of Δ-9-Tetrahydrocannabinol in Frequent Users of Cannabis. Neuropsychopharmacology 33, 2505–2516. https://doi.org/10.1038/sj.npp.1301643.

de Wit, H., Vicini, L., Childs, E., Sayla, M.A., Terner, J., 2007. Does stress reactivity or response to amphetamine predict smoking progression in young adults? A preliminary study. Pharmacol. Biochem. Behav. 86, 312–319. https://doi.org/https://doi.org/10.1016/j.pbb.2006.07.001.

Delitala, G., Grossman, A., Besser, M., 1983. Differential effects of opiate peptides and alkaloids on anterior pituitary hormone secretion. Neuroendocrinology 37, 275–279. https://doi.org/10.1159/000123558.

DeVito, E.E., Herman, A.I., Waters, A.J., Valentine, G.W., Sofuoglu, M., 2014. Subjective, Physiological and Cognitive Responses to Intravenous Nicotine: Effects of Sex and Menstrual Cycle Phase. Neuropsychopharmacology 39, 1431–1440. https://doi.org/10.1038/npp.2013.339.

Doan, S.N., Dich, N., Evans, G.W., 2014. Childhood cumulative risk and later allostatic load: mediating role of substance use. Health Psychol. 33, 1402–1409. https://doi.org/10.1037/a0034790.

Donny, E.C., Caggiula, A.R., Rose, C., Jacobs, K.S., Mielke, M.M., Sved, A.F., 2000. Differential effects of response-contingent and response-independent nicotine in rats. Eur. J. Pharmacol. 402, 231–240. https://doi.org/10.1016/S0014-2999(00)00532-X.

dos Santos, R.G., Valle, M., Bouso, J.C., Nomdedéu, J.F., Rodríguez-Espinosa, J., McIlhenny, E.H., Barker, S.A., Barbanoj, M.J., Riba, J., 2011. Autonomic, neuroendocrine, and immunological effects of ayahuasca: A comparative study with d-amphetamine. J. Clin. Psychopharmacol. 31, 717–726. https://doi.org/10.1097/JCP.0b013e31823607f6.

Dumont, G.J., Kramers, C., Sweep, F.C., Touw, D.J., van Hasselt, J.G., de Kam, M., van Gerven, J.M., Buitelaar, J.K., Verkes, R.J., 2009. Cannabis Coadministration Potentiates the Effects of "Ecstasy" on Heart Rate and Temperature in Humans. Clin. Pharmacol. Ther. 86, 160–166. https://doi.org/10.1038/clpt.2009.62.

Eisenberg, R.M., 1985. Effects of chronic treatment with diazepam, phenobarbital, or amphetamine on naloxone-precipitated morphine withdrawal. Drug Alcohol Depend. 15, 375–381.

Enoch, M.-A., 2011. The role of early life stress as a predictor for alcohol and drug dependence. Psychopharmacology (Berl) 214, 17–31. https://doi.org/10.1007/s00213-010-1916-6.
Errico, A.L., King, A.C., Lovallo, W.R., Parsons, O.A., 2002. Cortisol Dysregulation and Cognitive Impairment in Abstinent Male Alcoholics. Alcohol Clin. Exp. Res. 26, 1198–1204. https://doi.org/10.1111/j.1530-0277.2002.tb02656.x.
Esel, E., 2001. Plasma Levels of Beta-Endorphin, Adrenocorticotropic Hormone and Cortisol During Early and Late Alcohol Withdrawal. Alcohol Alcohol 36, 572–576. https://doi.org/10.1093/alcalc/36.6.572.
Evans, B.E., Greaves-Lord, K., Euser, A.S., Franken, I.H.A., Huizink, A.C., 2012. The relation between hypothalamic-pituitary-adrenal (HPA) axis activity and age of onset of alcohol use. Addiction 107, 312–322. https://doi.org/10.1111/j.1360-0443.2011.03568.x.
Feller, S., Vigl, M., Bergmann, M.M., Boeing, H., Kirschbaum, C., Stalder, T., 2014. Predictors of hair cortisol concentrations in older adults. Psychoneuroendocrinology 39, 132–140. https://doi.org/10.1016/j.psyneuen.2013.10.007.
Flanagan, J.C., Baker, N.L., McRae-Clark, A.L., Brady, K.T., Moran-Santa Maria, M.M., 2015. Effects of adverse childhood experiences on the association between intranasal oxytocin and social stress reactivity among individuals with cocaine dependence. Psychiatr. Res. 229, 94–100. https://doi.org/10.1016/j.psychres.2015.07.064.
Foltin, R.W., Fischman, M.W., 1990. The effects of combinations of intranasal cocaine, smoked marijuana, and task performance on heart rate and blood pressure. Pharmacol. Biochem. Behav. 36, 311–315. https://doi.org/10.1016/0091-3057(90)90409-B.
Foltin, R.W., Fischman, M.W., Pedroso, J.J., Pearlson, G.D., 1987. Marijuana and cocaine interactions in humans: Cardiovascular consequences. Pharmacol. Biochem. Behav. 28, 459–464. https://doi.org/10.1016/0091-3057(87)90506-5.
Foltin, R.W., Fischman, M.W., Pippen, P.A., Kelly, T.H., 1993. Behavioral effects of cocaine alone and in combination with ethanol or marijuana in humans. Drug Alcohol Depend. 32, 93–106. https://doi.org/10.1016/0376-8716(93)80001-U.
Foltin, R.W., Fischman, M.W., Levin, F.R., 1995. Cardiovascular effects of cocaine in humans: laboratory studies. Drug Alcohol Depend. 37, 193–210. https://doi.org/10.1016/0376-8716(94)01085-Y.
Foltin, R.W., Ward, A.S., Haney, M., Hart, C.L., Collins, E.D., 2003. The effects of escalating doses of smoked cocaine in humans. Drug Alcohol Depend. 70, 149–157. https://doi.org/10.1016/S0376-8716(02)00343-5.
Foulds, J., Stapleton, J.A., Bell, N., Swettenham, J., Jarvis, M.J., Russell, M.A.H., 1997. Mood and physiological effects of subcutaneous nicotine in smokers and never-smokers. Drug Alcohol Depend. 44, 105–115. https://doi.org/10.1016/S0376-8716(96)01327-0.
Fox, H., Sinha, R., 2014. The role of guanfacine as a therapeutic agent to address stress-related pathophysiology in cocaine-dependent individuals. Adv. Pharmacol. 69, 218–265. https://doi.org/10.1016/B978-0-12-420118-7.00006-8.
Fox, H.C., Anderson, G.M., Tuit, K., Hansen, J., Kimmerling, A., Siedlarz, K.M., Morgan, P.T., Sinha, R., 2012. Prazosin effects on stress- and cue-induced craving and stress response in alcohol-dependent individuals: preliminary findings. Alcohol Clin. Exp. Res. 36, 351–360. https://doi.org/10.1111/j.1530-0277.2011.01628.x.
Fox, H.C., Tuit, K.L., Sinha, R., 2013. Stress system changes associated with marijuana dependence may increase craving for alcohol and cocaine. Hum. Psychopharmacol. Clin. Exp. 28, 40–53. https://doi.org/10.1002/hup.2280.
Frederick, S.L., Reus, V.I., Ginsberg, D., Hall, S.M., Munoz, R.F., Ellman, G., 1998. Cortisol and response to dexamethasone as predictors or withdrawal distress and abstinence success in smokers. Biol. Psychiatry 43, 525–530. https://doi.org/10.1016/S0006-3223(97)00423-X.
Frias, J., Rodriguez, R., Torres, J.M., Ruiz, E., Ortega, E., 2000. Effects of acute alcohol intoxication on pituitary-gonadal axis hormones, pituitary-adrenal axis hormones, β-endorphin and prolactin in human adolescents of both sexes. Life Sci. 67, 1081–1086. https://doi.org/10.1016/S0024-3205(00)00702-5.
Fu, Y., Matta, S.G., Valentine, J.D., Sharp, B.M., 1997. Adrenocorticotropin Response and Nicotine-Induced Norepinephrine Secretion in the Rat Paraventricular Nucleus Are Mediated through Brainstem Receptors. Endocrinology 138, 1935–1943. https://doi.org/10.1210/endo.138.5.5122.
George, J.M., Reier, C.E., Lanese, R.R., Rower, J.M., 1974. Morphine Anesthesia Blocks Cortisol and Growth Hormone Response to Surgical Stress in Humans. J. Clin. Endocrinol. Metab. 38, 736–741. https://doi.org/10.1210/jcem-38-5-736.
Gerra, G., Ceresini, S., Esposito, A., Zaimovic, A., Moi, G., Bussandri, M., Raggi, M.A., Molina, E., 2003. Neuroendocrine and behavioural responses to opioid receptor-antagonist during heroin detoxification: Relationship with personality traits. Int. Clin. Psychopharmacol. 18, 261–269. https://doi.org/10.1097/00004850-200309000-00002.
Gerra, G., Somaini, L., Manfredini, M., Raggi, M.A., Saracino, M.A., Amore, M., Leonardi, C., Cortese, E., Donnini, C., 2014. Dysregulated responses to emotions among abstinent heroin users: Correlation with childhood neglect and addiction severity ☆. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 48, 220–228. https://doi.org/10.1016/j.pnpbp.2013.10.011.
Gianoulakis, C., Krishnan, B., Thavundayil, J., 1996. Enhanced Sensitivity of Pituitary βEndorphin to Ethanol in Subjects at High Risk of Alcoholism. Arch. Gen. Psychiatr. 53, 250. https://doi.org/10.1001/archpsyc.1996.01830030072011.
Ginty, A.T., 2013. Blunted responses to stress and reward: Reflections on biological disengagement? Int. J. Psychophysiol. 90, 90–94. https://doi.org/10.1016/j.ijpsycho.2013.06.008.
Goldstein, R.Z., Volkow, N.D., 2002. Drug addictions and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. Am. J. Psychiatry 159, 1642–1652. https://doi.org/10.1176/appi.ajp.159.10.1642.
Gourlay, S.G., Benowitz, N.L., 1997. Arteriovenous differences in plasma concentration of nicotine and catecholamines and related cardiovascular effects after smoking, nicotine nasal spray, and intravenous nicotine. Clin. Pharmacol. Ther. 62, 453–463. https://doi.org/10.1016/S0009-9236(97)90124-7.
Greenwald, M.K., 2018. Anti-stress neuropharmacological mechanisms and targets for addiction treatment: A translational framework. Neurobiol. Stress 9, 84–104. https://doi.org/10.1016/J.YNSTR.2018.08.003.
Grossman, A., Moult, P.J.A., Cunnah, D., Besser, M., 1986. Different opioid mechanisms are involved in the modulation of ACTH and gonadotrophin release in man. Neuroendocrinology 42, 357–360. https://doi.org/10.1159/000124463.
Grunberg, N.E., Popp, K.A., Bowen, D.J., Nespor, S.M., Winders, S.E., Eury, S.E., 1988. Effects of chronic nicotine administration on insulin, glucose, epinephrine, and norepinephrine. Life Sci. 42, 161–170.
Halbreich, U., Sachar, E.J., Asnis, G.M., Nathan, R.S., Halpern, F.S., 1981. Diurnal cortisol responses to dextroamphetamine in normal subjects. Psychoneuroendocrinology 6, 223–229. https://doi.org/10.1016/0306-4530(81)90031-7.
Hamidovic, A., Childs, E., Conrad, M., King, A., de Wit, H., 2010. Stress-induced changes in mood and cortisol release predict mood effects of amphetamine. Drug Alcohol Depend. 109, 175–180. https://doi.org/10.1016/j.drugalcdep.2009.12.029.
Haney, M., Ward, A.S., Gerra, G., Foltin, R.W., 2001. Neuroendocrine effects of d-fenfluramine and bromocriptine following repeated smoked cocaine in humans. Drug Alcohol Depend. 64, 63–73. https://doi.org/10.1016/S0376-8716(00)00232-5.
Haney, M., Malcolm, R.J., Babalonis, S., Nuzzo, P.A., Cooper, Z.D., Bedi, G., Gray, K.M., McRae-Clark, A., Lofwall, M.R., Sparenborg, S., Walsh, S.L., 2016. Oral Cannabidiol does not Alter the Subjective, Reinforcing or Cardiovascular Effects of Smoked Cannabis. Neuropsychopharmacology 41, 1974–1982. https://doi.org/10.1038/npp.2015.367.
Haney, M., Cooper, Z.D., Bedi, G., Herrmann, E., Comer, S.D., Reed, S.C., Foltin, R.W., Levin, F.R., 2018. Guanfacine decreases symptoms of cannabis withdrawal in daily cannabis smokers. Addict. Biol. https://doi.org/10.1111/adb.12621.
Harris, D.S., Reus, V.I., Wolkowitz, O.M., Mendelson, J.E., Jones, R.T., 2003. Altering cortisol level does not change the pleasurable effects of methamphetamine in humans. Neuropsychopharmacology 28, 1677–1684. https://doi.org/10.1038/sj.npp.1300223.
Harris, D.S., Reus, V.I., Wolkowitz, O., Jacob 3rd, P., Everhart, E.T., Wilson, M., Mendelson, J.E., Jones, R.T., 2006. Catecholamine response to methamphetamine is related to glucocorticoid levels but not to pleasurable subjective response. Pharmacopsychiatry 39, 100–108. https://doi.org/10.1055/s-2006-941483.
Hawley, R.J., Nemeroff, C.B., Bissette, G., Guidotti, A., Rawlings, R., Linnoila, M., 1994. Neurochemical Correlates of Sympathetic Activation during Severe Alcohol Withdrawal. Alcohol Clin. Exp. Res. 18, 1312–1316. https://doi.org/10.1111/j.1530-0277.1994.tb01429.x.
Heesch, C.M., Negus, B.H., Snyder, R.W., Eichhorn, E.J., Keffer, J.H., Risser, R.C., 1995. Effects of Cocaine on Cortisol Secretion in Humans. Am. J. Med. Sci. 310, 61–64. https://doi.org/10.1097/00000441-199508000-00004.
Henry, B.L., Minassian, A., Perry, W., 2012. Effect of methamphetamine dependence on heart rate variability. Addict. Biol. 17, 648–658. https://doi.org/10.1111/j.1369-1600.2010.00270.x.
Hill, P., Wynder, E.L., 1974. Smoking and cardiovascular disease. Effect of nicotine on the serum epinephrine and corticoids. Am. Heart J. 87, 491–496. https://doi.org/10.1016/0002-8703(74)90174-4.
Hoffman, W.E., McDonald, T., Berkowitz, R., 1998. Simultaneous increases in respiration and sympathetic function during opiate detoxification. J. Neurosurg. Anesthesiol. 10, 205–210. https://doi.org/10.1097/00008506-199810000-00001.
Holdstock, L., King, A.C., Wit, H., De Wit, H., 2000. Subjective and objective responses to ethanol in moderate/heavy and light social drinkers. Alcohol Clin. Exp. Res. 24, 789–794. https://doi.org/10.1111/j.1530-0277.2000.tb02057.x.
Hollister, L.E., Moore, F., Kanter, S., Noble, E., 1970. Δ1-Tetrahydrocannabinol, synhexyl and marijuana extract administered orally in man: Catecholamine excretion, plasma cortisol levels and platelet serotonin content. Psychopharmacologia 17, 354–360. https://doi.org/10.1007/BF00404241.
Howes, L.G., Reid, J.L., 1985. Changes in plasma free 3,4-dihydroxyphenylethylene glycol and noradrenaline levels after acute alcohol administration. Clin. Sci. (Lond.) 69, 423–428. https://doi.org/10.1042/cs0690423.
Huizink, A.C., Ferdinand, R.F., Ormel, J., Verhulst, F.C., 2006. Hypothalamic-pituitary-adrenal axis activity and early onset of cannabis use. Addiction 101, 1581–1588. https://doi.org/10.1111/j.1360-0443.2006.01570.x.
Inder, W.J., Joyce, P.R., Ellis, M.J., Evans, M.J., Livesey, J.H., Donald, R.A., 1995. The effects of alcoholism on the hypothalamic - pituitary - adrenal axis: interaction with endogenous opioid peptides. Clin. Endocrinol. 43 (3), 283–290.
Jacobs, D., Silverstone, T., Rees, L., 1989. The neuroendrocrine response to oral dextroamphetamine in normal subjects. Int. Clin. Psychopharmacol. 4, 135–147.
Jayaram-Lindström, N., Konstenius, M., Eksborg, S., Beck, O., Hammarberg, A., Franck, J., 2008. Naltrexone Attenuates the Subjective Effects of Amphetamine in Patients with Amphetamine Dependence. Neuropsychopharmacology 33, 1856–1863. https://doi.org/10.1038/sj.npp.1301572.
Justice, A.J.H., de Wit, H., 1999. Acute effects of d -amphetamine during the follicular and luteal phases of the menstrual cycle in women. Psychopharmacology (Berl) 145, 67–75. https://doi.org/10.1007/s002130051033.
Karakaya, O., Barutcu, I., Kaya, D., Esen, A.M., Saglam, M., Melek, M., Onrat, E., Turkmen, M., Esen, O.B., Kaymaz, C., 2007. Acute effect of cigarette smoking on heart rate variability. Angiology 58, 620–624. https://doi.org/10.1177/0003319706294555.
Kennedy, A.P., Epstein, D.H., Jobes, M.L., Agage, D., Tyburski, M., Phillips, K.A., Ali, A.A., Bari, R., Hossain, S.M., Hovsepian, K., Rahman, M.M., Ertin, E., Kumar, S., Preston, K.L., 2015. Continuous in-the-field measurement of heart rate: Correlates of drug use, craving, stress, and mood in polydrug users. Drug Alcohol Depend. 151, 159–166. https://doi.org/10.1016/j.drugalcdep.2015.03.024.

Kienbaum, P., Thurauf, N., Michel, M.C., Scherbaum, N., Gastpar, M., Peters, J., 1998. Profound Increase in Epinephrine Concentration in Plasma and Cardiovascular Stimulation after mu-Opioid Receptor Blockade in Opioid-addicted Patients during Barbiturate-induced Anesthesia for Acute Detoxification. Anesthesiology 88.

King, A., Munisamy, G., de Wit, H., Lin, S., 2006. Attenuated cortisol response to alcohol in heavy social drinkers. Int. J. Psychophysiol. 59, 203–209. https://doi.org/10.1016/j.ijpsycho.2005.10.008.

King, G.R., Ernst, T., Deng, W., Stenger, A., Gonzales, R.M.K., Nakama, H., Chang, L., 2011. Altered Brain Activation During Visuomotor Integration in Chronic Active Cannabis Users: Relationship to Cortisol Levels. J. Neurosci. 31, 17923–17931. https://doi.org/10.1523/JNEUROSCI.4148-11.2011.

King, A.C., Hasin, D., O'Connor, S.J., McNamara, P.J., Cao, D., 2016. A Prospective 5-Year Re-examination of Alcohol Response in Heavy Drinkers Progressing in Alcohol Use Disorder. Biol. Psychiatry 79, 489–498. https://doi.org/10.1016/J.BIOPSYCH.2015.05.007.

Knych, E.T., Eisenberg, R.M., 1979. Effect of amphetamine on plasma corticosterone in the conscious rat. Neuroendocrinology 29, 110–118. https://doi.org/10.1159/000122912.

Kobayashi, F., Watanabe, T., Akamatsu, Y., Furui, H., Tomita, T., Ohashi, R., Hayano, J., 2005. Acute effects of cigarette smoking on the heart rate variability of taxi drivers during work. Scand. J. Work. Environ. Health 31, 360–366. https://doi.org/10.5271/sjweh.919.

Kollins, S.H., Rush, C.R., 2002. Sensitization to the cardiovascular but not subject-rated effects of oral cocaine in humans. Biol. Psychiatry 51, 143–150. https://doi.org/10.1016/S0006-3223(01)01288-4.

Kollins, S.H., Schoenfelder, E.N., English, J.S., Holdaway, A., Van Voorhees, E., O'Brien, B.R., Dew, R., Chrisman, A.K., 2015. An exploratory study of the combined effects of orally administered methylphenidate and delta-9-tetrahydrocannabinol (THC) on cardiovascular function, subjective effects, and performance in healthy adults. J. Subst. Abuse Treat. 48, 96–103. https://doi.org/10.1016/J.JSAT.2014.07.014.

Kosten, T.R., Kosten, T.A., McDougle, C.J., Hameedi, F.A., McCance, E.F., Rosen, M.I., Oliveto, A.H., Price, L.H., 1996. Gender differences in response to intranasal cocaine administration to humans. Biol. Psychiatry 39, 147–148. https://doi.org/10.1016/0006-3223(95)00386-X.

Kubena, R.K., Perhach, J.L., Barry, H., 1971. Corticosterone elevation mediated centrally by Δ1-tetrahydrocannabinol in rats. Eur. J. Pharmacol. 14, 89–92. https://doi.org/10.1016/0014-2999(71)90128-2.

Kuhn, C., Francis, R., 1997. Gender difference in cocaine-induced HPA axis activation. Neuropsychopharmacology 16, 399–407. https://doi.org/10.1016/S0893-133X(96)00278-3.

Latson, T.W., McCarroll, S.M., Mirhej, M.A., Hyndman, V.A., Whitten, C.W., Lipton, J.M., 1992. Effects of three anesthetic induction techniques on heart rate variability. J. Clin. Anesth 4 (4), 265–276. https://doi.org/10.1016/0952-8180(92)90127-M.

Lê, A.D., Funk, D., Juzytsch, W., Coen, K., Navarre, B.M., Cifani, C., Shaham, Y., 2011. Effect of prazosin and guanfacine on stress-induced reinstatement of alcohol and food seeking in rats. Psychopharmacology (Berl) 218, 89–99. https://doi.org/10.1007/s00213-011-2178-7.

Le Moal, M., Koob, G.F., 2007. Drug addiction: Pathways to the disease and pathophysiological perspectives. Eur. Neuropsychopharmacol. 17, 377–393. https://doi.org/10.1016/J.EURONEURO.2006.10.006.

Levy, A.D., Li, Q., Kerr, J.E., Rittenhouse, P.A., Milonas, G., Cabrera, T.M., Battaglia, G., Alvarez Sanz, M.C., Van De Kar, L.D., 1991. Cocaine-Induced Elevation of Plasma Adrenocorticotropin Hormone and Corticosterone Is Mediated by Serotonergic Neurons 1. J. Pharmacol. Exp. Therapeut. 259, 495–500.

Lijffijt, M., Hu, K., Swann, A.C., 2014. Stress Modulates Illness-Course of Substance Use Disorders: A Translational Review. Front. Psychiatry 5, 83. https://doi.org/10.3389/fpsyt.2014.00083.

Lindgren, J.-E., Ohlsson, A., Agurell, S., Hollister, L., Gillespie, H., 1981. Clinical Effects and Plasma Levels of A 9-Tetrahydrocannabinol (A 9-THC) in Heavy and Light Users of Cannabis, Psychopharmacology. Springer-Verlag. https://doi.org/10.1007/BF00427095.

Livezey, G.T., Balabkins, N., Vogel, W.H., 1987. The effect of ethanol (alcohol) and stress on plasma catecholamine levels in individual female and male rats. Neuropsychobiology 17, 193–198. https://doi.org/10.1159/000118364.

Longo, D.L., Volkow, N.D., Koob, G.F., McLellan, A.T., 2016. Neurobiologic Advances from the Brain Disease Model of Addiction. N. Engl. J. Med. 374, 363–371. https://doi.org/10.1056/NEJMra1511480.

Lovallo, W.R., 2006. Cortisol secretion patterns in addiction and addiction risk. Int. J. Psychophysiol. 59, 195–202. https://doi.org/10.1016/j.ijpsycho.2005.10.007.

Lovallo, W.R., 2013. Early life adversity reduces stress reactivity and enhances impulsive behavior: implications for health behaviors. Int. J. Psychophysiol. 90, 8–16. https://doi.org/10.1016/j.ijpsycho.2012.10.006.

Lutfy, K., Aimiuwu, O., Mangubat, M., Shin, C.-S., Nerio, N., Gomez, R., Liu, Y., Friedman, T.C., 2012. Nicotine stimulates secretion of corticosterone via both CRH and AVP receptors. J. Neurochem. 120, 1108–1116.

Lynch, W.J., Sughondhabirom, A., Pittman, B., Gueorguieva, R., Kalayasiri, R., Joshua, D., Morgan, P., Coric, V., Malison, R.T., 2006. A paradigm to investigate the regulation of cocaine self-administration in human cocaine users: a randomized trial. Psychopharmacology (Berl) 185, 306–314. https://doi.org/10.1007/s00213-006-0323-5.

Lynch, W.J., Kalayasiri, R., Sughondhabirom, A., Pittman, B., Coric, V., Morgan, P.T., Malison, R.T., 2008. Subjective responses and cardiovascular effects of self-administered cocaine in cocaine-abusing men and women. Addict. Biol. 13, 403–410. https://doi.org/10.1111/j.1369-1600.2008.00115.x.

Manetti, L., Cavagnini, F., Martino, E., Ambrogio, A., 2014. Effects of cocaine on the hypothalamic–pituitary–adrenal axis. J. Endocrinol. Invest. 37, 701–708. https://doi.org/10.1007/s40618-014-0091-8.

Marinelli, M., Piazza, P.V., 2002. Interaction between glucocorticoid hormones, stress and psychostimulant drugs. Eur. J. Neurosci. 16, 387–394. https://doi.org/10.1046/j.1460-9568.2002.02089.x.

Martinez, D., Narendran, R., 2010. Imaging neurotransmitter release by drugs of abuse. Curr. Top. Behav. Neurosci. 3, 219–245. https://doi.org/10.1007/7854_2009_34.

Martinez, D., Carpenter, K.M., Liu, F., Slifstein, M., Broft, A., Friedman, A.C., Kumar, D., Van Heertum, R., Kleber, H.D., Nunes, E., 2011. Imaging dopamine transmission in cocaine dependence: link between neurochemistry and response to treatment. Am. J. Psychiatry 168, 634–641. https://doi.org/10.1176/appi.ajp.2010.10050748.

Martins, S.S., Segura, L.E., Santaella-Tenorio, J., Perlmutter, A., Fenton, M.C., Cerdá, M., Keyes, K.M., Ghandour, L.A., Storr, C.L., Hasin, D.S., 2017. Prescription opioid use disorder and heroin use among 12-34 year-olds in the United States from 2002 to 2014. Addict. Beyond Behav. 65, 236–241. https://doi.org/10.1016/j.addbeh.2016.08.033.

Martín-Calderón, J.L., Muñoz, R.M., Villanúa, M.A., del Arco, I., Moreno, J.L., de Fonseca, F.R., Navarro, M., 1998. Characterization of the acute endocrine actions of (−)-11-hydroxy-Δ8-tetrahydrocannabinol-dimethylheptyl (HU-210), a potent synthetic cannabinoid in rats. Eur. J. Pharmacol. 344, 77–86. https://doi.org/10.1016/S0014-2999(97)01560-4.

Matta, S.G., Singh, J., Sharp, B.M., 1990. Catecholamines mediate nicotine-induced adrenocorticotropin secretion via α-adrenergic receptors. Endocrinology 127, 1646–1655. https://doi.org/10.1210/endo-127-4-1646.

McDonald, T., Hoffman, W.E., Berkowitz, R., Cunningham, F., Cooke, B., 1999. Heart rate variability and plasma catecholamines in patients during opioid detoxification. J. Neurosurg. Anesthesiol. 11, 195–199.

McDougle, C.J., Black, J.E., Malison, R.T., Zimmermann, R.C., Kosten, T.R., Heninger, G.R., Price, L.H., 1994. Noradrenergic dysregulation during discontinuation of cocaine use in addicts. Arch. Gen. Psychiatr. 51, 713–719.

McKee, S. a, Sinha, R., Weinberger, A.H., Sofuoglu, M., Harrison, E.L.R., Lavery, M., Wanzer, J., 2011. Stress decreases the ability to resist smoking and potentiates smoking intensity and reward. J. Psychopharmacol. 25, 490–502. https://doi.org/10.1177/0269881110376694.

McRae-Clark, A.L., Carter, R.E., Price, K.L., Baker, N.L., Thomas, S., Saladin, M.E., Giarla, K., Nicholas, K., Brady, K.T., 2011. Stress- and cue-elicited craving and reactivity in marijuana-dependent individuals. Psychopharmacology (Berl) 218, 49–58. https://doi.org/10.1007/s00213-011-2376-3.

Mello, N.K., 2010. Hormones, nicotine, and cocaine: clinical studies. Horm. Behav. 58, 57–71. https://doi.org/10.1016/j.yhbeh.2009.10.003.

Mendelson, J., Stein, S., 1966. Serum Cortisol Levels in Alcoholic and Nonalcoholic Subjects During Experimentally Induced Ethanol Intoxication. Psychosom. Med. 28, 616–626.

Mendelson, J.H., Meyer, R.E., Ellingboe, J., Mirin, S.M., McDougle, M., 1975. Effects of heroin and methadone on plasma cortisol and testosterone. J. Pharmacol. Exp. Therapeut. 195.

Mendelson, J.H., Teoh, S.K., Lange, U., Mello, N.K., Weiss, R., Skupny, A., Ellingboe, J., 1988. Anterior pituitary, adrenal, and gonadal hormones during cocaine withdrawal. Am. J. Psychiatry 145, 1094–1098. https://doi.org/10.1176/ajp.145.9.1094.

Mendelson, J.H., Sholar, M.B., Goletiani, N., Siegel, A.J., Mello, N.K., 2005. Effects of low- and high-nicotine cigarette smoking on mood states and the HPA axis in men. Neuropsychopharmacology 30, 1751–1763. https://doi.org/10.1038/sj.npp.1300753.

Mendelson, J.H., Goletiani, N., Sholar, M.B., Siegel, A.J., Mello, N.K., 2008. Effects of Smoking Successive Low- and High-Nicotine Cigarettes on Hypothalamic–Pituitary–Adrenal Axis Hormones and Mood in Men. Neuropsychopharmacology 33, 749–760. https://doi.org/10.1038/sj.npp.1301455.

Milivojevic, V., Sinha, R., 2018. Central and Peripheral Biomarkers of Stress Response for Addiction Risk and Relapse Vulnerability. Trends Mol. Med. https://doi.org/10.1016/j.molmed.2017.12.010.

Minami, J., Ishimitsu, T., Matsuoka, H., 1999. Effects of Smoking Cessation on Blood Pressure and Heart Rate Variability in Habitual Smokers. Hypertension 33, 586–590. https://doi.org/10.1161/01.HYP.33.1.586.

Moldow, R.L., Fischman, A.J., 1987. Cocaine induced secretion of ACTH, beta-endorphin, and corticosterone. Peptides 8, 819–822. https://doi.org/10.1016/0196-9781(87)90065-9.

Morse, D.E., 1989. Neuroendocrine responses to nicotine and stress: enhancement of peripheral stress responses by the administration of nicotine. Psychopharmacology (Berl) 98, 539–543. https://doi.org/https://doi.org/10.1007/BF00441956.

Motaghinejad, M., Bangash, M.Y., Motaghinejad, O., 2015. Attenuation of alcohol withdrawal syndrome and blood cortisol level with forced exercise in comparison with diazepam. Acta Med. Iran. 53, 312–317.

Munro, C.A., McCaul, M.E., Wong, D.F., Oswald, L.M., Zhou, Y., Brasic, J., Kuwabara, H., Kumar, A., Alexander, M., Ye, W., Wand, G.S., 2006. Sex Differences in Striatal Dopamine Release in Healthy Adults. Biol. Psychiatry 59, 966–974. https://doi.org/10.1016/J.BIOPSYCH.2006.01.008.

Naber, D., Pickar, D., Davis, G.C., Cohen, R.M., Jimerson, D.C., Elchisak, M.A., Defraites, E.G., Kalin, N.H., Risch, S.C., Buchsbaum, M.S., 1981. Naloxone effects on beta-endorphin, cortisol, prolactin, growth hormone, HVA and MHPG in plasma of normal volunteers. Psychopharmacology (Berl) 74, 125–128.

Nagano-Saito, A., Dagher, A., Booij, L., Gravel, P., Welfeld, K., Casey, K.F., Leyton, M., Benkelfat, C., 2013. Stress-induced dopamine release in human medial prefrontal cortex-18F-fallypride/PET study in healthy volunteers. Synapse 67, 821–830. https://doi.org/10.1002/syn.21700.

Nava, F., Caldiroli, E., Premi, S., Lucchini, A., 2006. Relationship between plasma cortisol levels, withdrawal symptoms and craving in abstinent and treated heroin addicts. J. Addict. Dis. 25, 9–16. https://doi.org/10.1300/J069v25n02_02.

Nurnberger, J.I., Simmons-Alling, S., Kessler, L., Jimerson, S., Schreiber, J., Hollander, E., Tamminga, C.A., Nadi, N.S., Goldstein, D.S., Gershon, E.S., 1984. Separate mechanisms for behavioral, cardiovascular, and hormonal responses to dextroamphetamine in man. Psychopharmacology (Berl) 84, 200–204. https://doi.org/10.1007/BF00427446.

Okada, S., Shimizu, T., Yokotani, K., 2003. Extrahypothalamic corticotropin-releasing hormone mediates (−)-nicotine-induced elevation of plasma corticosterone in rats. Eur. J. Pharmacol. 473, 217–223. https://doi.org/10.1016/S0014-2999(03)01966-6.

Oswald, L.M., Wong, D.F., McCaul, M., Zhou, Y., Kuwabara, H., Choi, L., Brasic, J., Wand, G.S., 2005. Relationships among ventral striatal dopamine release, cortisol secretion, and subjective responses to amphetamine. Neuropsychopharmacology 30, 821–832. https://doi.org/10.1038/sj.npp.1300667.

Oswald, L.M., Wand, G.S., Kuwabara, H., Wong, D.F., Zhu, S., Brasic, J.R., 2014. History of childhood adversity is positively associated with ventral striatal dopamine responses to amphetamine. Psychopharmacology (Berl) 231, 2417–2433. https://doi.org/10.1007/s00213-013-3407-z.

Parrott, A.C.C., Sands, H.R.R., Jones, L., Clow, A., Evans, P., Downey, L.A.A., Stalder, T., 2014. Increased cortisol levels in hair of recent Ecstasy/MDMA users. Eur. Neuropsychopharmacol. 24, 369–374.

Perkins, K.A., Coddington, S.B., Karelitz, J.L., Jetton, C., Scott, J.A., Wilson, A.S., Lerman, C., 2009. Variability in initial nicotine sensitivity due to sex, history of other drug use, and parental smoking. Drug Alcohol Depend. 99, 47–57. https://doi.org/10.1016/J.DRUGALCDEP.2008.06.017.

Perman, E.S., 1960. The Effect of Ethyl Alcohol on the Secretion from the Adrenal Medulla of the Cat. Acta Physiol. Scand. 48, 323–328. https://doi.org/10.1111/j.1748-1716.1960.tb01866.x.

Pomerleau, O.F., Pomerleau, C.S., 1990. Cortisol response to a psychological stressor and/or nicotine. Pharmacol. Biochem. Behav. 36, 211–213. https://doi.org/https://doi.org/10.1016/0091-3057%2890%2990153-9.

Pruessner, J.C., Champagne, F., Meaney, M.J., Dagher, A., 2004. Dopamine release in response to a psychological stress in humans and its relationship to early life maternal care: a positron emission tomography study using [11C]raclopride. J. Neurosci. 24, 2825–2831. https://doi.org/10.1523/JNEUROSCI.3422-03.2004.

Puder, M., Weidenfeld, J., Chowers, I., Nir, I., Conforti, N., Siegel, R.A., 1982. Corticotrophin and corticosterone secretion following Δ1-tetrahydrocannabinol, in intact and in hypothalamic deafferentated male rats. Exp. Brain Res. 46, 85–88. https://doi.org/10.1007/BF00238101.

Quintana, D.S., McGregor, I.S., Guastella, A.J., Malhi, G.S., Kemp, A.H., 2013. A Meta-Analysis on the Impact of Alcohol Dependence on Short-Term Resting-State Heart Rate Variability: Implications for Cardiovascular Risk. Alcohol Clin. Exp. Res. 37, 23–29. https://doi.org/10.1111/j.1530-0277.2012.01913.x.

Ramchandani, V.A., Flury, L., Morzorati, S.L., Kareken, D., Blekher, T., Foroud, T., Li, T.-K., O'Connor, S., 2002. Recent drinking history: association with family history of alcoholism and the acute response to alcohol during a 60 mg% clamp. J. Stud. Alcohol 63, 734–744. https://doi.org/10.15288/jsa.2002.63.734.

Ramesh, D., Haney, M., Cooper, Z.D., 2013. Marijuana's dose-dependent effects in daily marijuana smokers. Exp. Clin. Psychopharmacol 21, 287–293. https://doi.org/10.1037/a0033661.

Ranganathan, M., Braley, G., Pittman, B., Cooper, T., Perry, E., Krystal, J., D'Souza, D.C., 2009. The effects of cannabinoids on serum cortisol and prolactin in humans. Psychopharmacology (Berl) 203, 737–744. https://doi.org/10.1007/s00213-008-1422-2.

Reid, M.S., Flammino, F., Howard, B., Nilsen, D., Prichep, L.S., 2006. Topographic imaging of quantitative EEG in response to smoked cocaine self-administration in humans. Neuropsychopharmacology 31, 872–884. https://doi.org/10.1038/sj.npp.1300888.

Richard, C., Scoti, C., Russell, B., 1986. Influence of Stage of the Estrous of Luteinizing Hormone , Cycle on Endogenous and Cortisol Opioid Modulation in the Gilt ' Secretion. Biol. Reprod. 35, 1162–1167. https://doi.org/10.1095/biolreprod35.5.1162.

Richardson, H.N., Lee, S.Y., O'Dell, L.E., Koob, G.F., Rivier, C.L., 2008. Alcohol self-administration acutely stimulates the hypothalamic-pituitary- adrenal axis, but alcohol dependence leads to a dampened neuroendocrine state. Eur. J. Neurosci. 28, 1641–1653. https://doi.org/10.1111/j.1460-9568.2008.06455.x.

Risher-Flowers, D., Adinoff, B., Ravitz, B., Bone, G., Martin, P., Nutt, D., Linnoila, M., 1988. Circadian rhythms of cortisol during alcohol withdrawal. Adv. Alcohol Subst. Abuse 7, 37–41. https://doi.org/10.1300/J251v07n03_06.

Rittmaster, R.S., Cutler, G.B., Sobel, D.0, Goldstein, D.S., Koppelman, M.C.S., Loriaux, D.L., Chrousos, G.P., 1985. Morphine Inhibits the Pituitary-Adrenal Response to Ovine Corticotropin-Releasing Hormone in Normal Subjects*. J. Clin. Endocrinol. Metabol.

Romanowicz, M., Schmidt, J.E., Bostwick, J.M., Mrazek, D.A., Karpyak, V.M., 2011. Changes in heart rate variability associated with acute alcohol consumption: Current knowledge and implications for practice and research. Alcohol Clin. Exp. Res. 35, 1092–1105. https://doi.org/10.1111/j.1530-0277.2011.01442.x.

Rook, E.J., Van Ree, J.M., Van Den Brink, W., Hillebrand, M.J.X., Huitema, A.D.R., Hendriks, V.M., Beijnen, J.H., 2006. Pharmacokinetics and pharmacodynamics of high doses of pharmaceutically prepared heroin, by intravenous or by inhalation route in opioid-dependent patients. Basic Clin. Pharmacol. Toxicol. 98, 86–96. https://doi.org/10.1111/j.1742-7843.2006.pto_233.x.

Rushen, J., Schwarze, N., Ladewig, J., Foxcroft, G., 1993. Opioid modulation of the effects of repeated stress on ACTH, cortisol, prolactin, and growth hormone in pigs. Physiol. Behav. 53, 923–928. https://doi.org/10.1016/0031-9384(93)90270-.

Sachar, E.J., Asnis, G., Nathan, R.S., Halbreich, U., Tabrizi, M.A., Halpern, F.S., 1980. Dextroamphetamine and Cortisol in Depression. Arch. Gen. Psychiatr. 37, 755. https://doi.org/10.1001/archpsyc.1980.01780200033003.

Saphier, D., Welch, J.E., Farrar, G.E., Goeders, N.E., 1993. Effects of intracerebroventricular and intrahypothalamic cocaine administration on adrenocortical secretion. Neuroendocrinology 57, 54–62. https://doi.org/10.1159/000126342.

Sarnyai, Z., Bíró, É., Penke, B., Telegdy, G., 1992. The cocaine-induced elevation of plasma corticosterone is mediated by endogenous corticotropin-releasing factor (CRF) in rats. Brain Res. 589, 154–156. https://doi.org/10.1016/0006-8993(92)91176-F.

Schuckit, M.A., Tsuang, J.W., Anthenelli, R.M., Tipp, J.E., Nurnberger, J.I., 1996. Alcohol challenges in young men from alcoholic pedigrees and control families: a report from the COGA project. J. Stud. Alcohol 57, 368–377. https://doi.org/10.15288/jsa.1996.57.368.

Seyler, L.E., Fertig, J., Pomerleau, O., Hunt, D., Parker, K., 1984. The effects of smoking on acth and cortisol secretion. Life Sci. 34, 57–65. https://doi.org/10.1016/0024-3205(84)90330-8.

Sharma, J., Rathnayaka, N., Green, C., Moeller, F.G., Schmitz, J.M., Shoham, D., Dougherty, A.H., 2016. Bradycardia as a Marker of Chronic Cocaine Use: A Novel Cardiovascular Finding. Behav. Med. 42, 1–8. https://doi.org/10.1080/08964289.2014.897931.

Shi, J., Li, S., Zhang, X., Wang, X., Foll, B. Le, Zhang, X.-Y., Kosten, T.R., Lu, L., 2009. Time-Dependent Neuroendocrine Alterations and Drug Craving during the First Month of Abstinence in Heroin Addicts. Am. J. Drug Alcohol Abuse 35, 267–272. https://doi.org/10.1080/00952990902933878.

Shiffman, S., Zettler-Segal, M., Kassel, J., Paty, J., Benowitz, N.L., O'Brien, G., 1992. Nicotine elimination and tolerance in non-dependent cigarette smokers. Psychopharmacology (Berl) 109, 449–456. https://doi.org/10.1007/BF02247722.

Sinha, R., 2001. How does stress increase risk of drug abuse and relapse? Psychopharmacology (Berl) 158, 343–359. https://doi.org/10.1007/s002130100917.

Sinha, R., 2008. Chronic stress, drug use, and vulnerability to addiction. Ann. N. Y. Acad. Sci. 1141, 105–130. https://doi.org/10.1196/annals.1441.030.

Sinha, R., 2011. New findings on biological factors predicting addiction relapse vulnerability. Curr. Psychiatr. Rep. 13, 398–405. https://doi.org/10.1007/s11920-011-0224-0.

Sinha, R., 2013. The clinical neurobiology of drug craving. Curr. Opin. Neurobiol. https://doi.org/10.1016/j.conb.2013.05.001.

Sinha, R., Li, C.S.R., 2007. Imaging stress- and cue-induced drug and alcohol craving: association with relapse and clinical implications. Drug Alcohol Rev. 26, 25–31. https://doi.org/10.1080/09595230601036960.

Sinha, R., Garcia, M., Paliwal, P., Kreek, M.J., Rounsaville, B.J., 2006. Stress-induced cocaine craving and hypothalamic-pituitary-adrenal responses are predictive of cocaine relapse outcomes. Arch. Gen. Psychiatr. 63, 324–331. https://doi.org/10.1001/archpsyc.63.3.324.

Sinha, R., Lacadie, C.M., Constable, R.T., Seo, D., 2016. Dynamic neural activity during stress signals resilient coping. Proc. Natl. Acad. Sci. 113, 8837–8842. https://doi.org/10.1073/pnas.1600965113.

Sjoberg, N., Saint, D.A., 2011. A Single 4 mg Dose of Nicotine Decreases Heart Rate Variability in Healthy Nonsmokers: Implications for Smoking Cessation Programs. Nicotine Tob. Res. 13, 369–372. https://doi.org/10.1093/ntr/ntr004.

Söderpalm, A., Nikolayev, L., de Wit, H., 2003. Effects of stress on responses to methamphetamine in humans. Psychopharmacology (Berl) 170, 188–199. https://doi.org/10.1007/s00213-003-1536-5.

Sofuoglu, M., Mooney, M., 2009. Subjective Responses to Intravenous Nicotine: Greater Sensitivity in Women Than in Men. Exp. Clin. Psychopharmacol 17, 63–69. https://doi.org/10.1037/a0015297.

Sofuoglu, M., Dudish-Poulsen, S., Nelson, D., Pentel, P.R., Hatsukami, D.K., 1999. Sex and menstrual cycle differences in the subjective effects from smoked cocaine in humans. Exp. Clin. Psychopharmacol 7, 274–283. https://doi.org/10.1037/1064-1297.7.3.274.

Sofuoglu, M., Nelson, D., Babb, D.A., Hatsukami, D.K., 2001. Intravenous cocaine increases plasma epinephrine and norepinephrine in humans. Pharmacol. Biochem. Behav. 68, 455–459. https://doi.org/10.1016/S0091-3057(01)00482-8.

Sofuoglu, M., Herman, A.I., Nadim, H., Jatlow, P., 2012. Rapid Nicotine Clearance is Associated with Greater Reward and Heart Rate Increases from Intravenous Nicotine. Neuropsychopharmacology 37, 1509–1516. https://doi.org/10.1038/npp.2011.336.

Somaini, L., Manfredini, M., Amore, M., Zaimovic, A., Raggi, M.A., Leonardi, C., Gerra, M.L., Donnini, C., Gerra, G., 2012. Psychobiological responses to unpleasant emotions in cannabis users. Eur. Arch. Psychiatry Clin. Neurosci. 262, 47–57. https://doi.org/https://doi.org/10.1007/s00406-011-0223-5.

Spronk, D.B., van Wel, J.H.P., Ramaekers, J.G., Verkes, R.J., 2013. Characterizing the cognitive effects of cocaine: A comprehensive review. Neurosci. Biobehav. Rev. 37, 1838–1859. https://doi.org/10.1016/J.NEUBIOREV.2013.07.003.

Starcke, K., van Holst, R.J., van den Brink, W., Veltman, D.J., Goudriaan, A.E., 2013. Physiological and endocrine reactions to psychosocial stress in alcohol use disorders: Duration of abstinence matters. Alcohol Clin. Exp. Res. 37, 1343–1350.

Stokes, P.E., 1973. Adrenocortical activation in alcoholics. Ann. N. Y. Acad. Sci. 215, 77–83. https://doi.org/10.1111/j.1749-6632.1973.tb28251.x.

Stormark, K.M., Laberg, J.C., Nordby, H., Hugdahl, K., 1998. Heart rate responses indicate locked-in attention in alcoholics immediately prior to drinking. Addict. Behav. 23, 251–255. https://doi.org/10.1016/S0306-4603(97)00026-9.

Strougo, A., Zuurman, L., Roy, C., Pinquier, J., van Gerven, J., Cohen, A., Schoemaker, R., 2008. Modelling of the concentration—effect relationship of THC on central nervous system parameters and heart rate — insight into its mechanisms of action and a tool for clinical research and development of cannabinoids. J. Psychopharmacol. 22, 717–726. https://doi.org/10.1177/0269881108089870.

Suemaru, S., Dallman, M.F., Darlington, D.N., Cascio, C.S., Shinsako, J., 1989. Role of alpha-adrenergic mechanism in effects of morphine on the hypothalamo-pituitary-

adrenocortical and cardiovascular systems in the rat. Neuroendocrinology 49, 181–190. https://doi.org/10.1159/000125112.
Sutker, P.B., Goist, K.C., King, A.R., 1987. Acute Alcohol Intoxication in Women: Relationship to Dose and Menstrual Cycle Phase. Alcohol Clin. Exp. Res. 11, 74–79. https://doi.org/10.1111/j.1530-0277.1987.tb01266.x.
Swerdlow, N.R., Koob, G.F., Cador, M., Lorang, M., Hauger, R.L., 1993. Pituitary-adrenal axis responses to acute amphetamine in the rat. Pharmacol. Biochem. Behav. 45, 629–637. https://doi.org/10.1016/0091-3057(93)90518-X.
Tapper, E.B., Parikh, N.D., 2018. Mortality due to cirrhosis and liver cancer in the United States, 1999-2016: observational study. BMJ 362, k2817. https://doi.org/10.1136/BMJ.K2817.
Thayer, J.F., Hall, M., Sollers, J.J., Fischer, J.E., 2006. Alcohol use, urinary cortisol, and heart rate variability in apparently healthy men: Evidence for impaired inhibitory control of the HPA axis in heavy drinkers. Int. J. Psychophysiol. 59, 244–250. https://doi.org/10.1016/j.ijpsycho.2005.10.013.
Tizabi, Y., Copeland, R.L., Louis, V.A., Taylor, R.E., 2002. Effects of Combined Systemic Alcohol and Central Nicotine Administration into Ventral Tegmental Area on Dopamine Release in the Nucleus Accumbens. Alcohol Clin. Exp. Res. 26, 394–399. https://doi.org/10.1111/j.1530-0277.2002.tb02551.x.
Tsuji, H., Venditti, F.J., Manders, E.S., Evans, J.C., Larson, M.G., Feldman, C.L., Levy, D., 1996. Determinants of heart rate variability. J. Am. Coll. Cardiol. 28, 1539–1546. https://doi.org/10.1016/S0735-1097(96)00342-7.
US Department of Healt and Human Services, 2016. Facing addiction in America: The Surgeon General's report on alcohol, drugs, and health. HHS, Washington, DC.
Välimäki, M.J., Härkönen, M., Peter Eriksson, C.J., Ylikahri, R.H., 1984. Sex hormones and adrenocortical steroids in men acutely intoxicated with ethanol. Alcohol 1, 89–93. https://doi.org/10.1016/0741-8329(84)90043-0.
Van Dam, N.T., Rando, K., Potenza, M.N., Tuit, K., Sinha, R., 2014. Childhood Maltreatment, Altered Limbic Neurobiology, and Substance Use Relapse Severity via Trauma-Specific Reductions in Limbic Gray Matter Volume. JAMA Psychiatry 71, 917. https://doi.org/10.1001/jamapsychiatry.2014.680.
Van Hedger, K., Bershad, A.K., de Wit, H., 2017. Pharmacological challenge studies with acute psychosocial stress. Psychoneuroendocrinology 85, 123–133. https://doi.org/10.1016/j.psyneuen.2017.08.020.
Vandrey, R., Umbricht, A., Strain, E.C., 2011. Increased blood pressure after abrupt cessation of daily cannabis use. J. Addiction Med. 5, 16–20. https://doi.org/10.1097/ADM.0b013e3181d2b309.
Vandrey, R., Stitzer, M.L., Mintzer, M.Z., Huestis, M.A., Murray, J.A., Lee, D., 2013. The dose effects of short-term dronabinol (oral THC) maintenance in daily cannabis users. Drug Alcohol Depend. 128, 64–70. https://doi.org/10.1016/J.DRUGALCDEP.2012.08.001.
Vongpatanasin, W., Taylor, J.A., Victor, R.G., 2004. Effects of cocaine on heart rate variability in healthy subjects. Am. J. Cardiol. 93, 385–388. https://doi.org/10.1016/J.AMJCARD.2003.10.028.
Vuong, C., Van Uum, S.H.M., O'Dell, L.E., Lutfy, K., Friedman, T.C., 2010. The Effects of Opioids and Opioid Analogs on Animal and Human Endocrine Systems. Endocr. Rev. 31, 98–132. https://doi.org/10.1210/er.2009-0009.
Walsh, S.L., Haberny, K.A., Bigelow, G.E., 2000. Modulation of intravenous cocaine effects by chronic oral cocaine in humans. Psychopharmacology (Berl) 150, 361–373. https://doi.org/10.1007/s002130000439.
Walsh, S.L., Stoops, W.W., Moody, D.E., Lin, S.-N., Bigelow, G.E., 2009. Repeated dosing with oral cocaine in humans: assessment of direct effects, withdrawal, and pharmacokinetics. Exp. Clin. Psychopharmacol 17, 205–216. https://doi.org/10.1037/a0016469.
Walter, M., Wiesbeck, G.A., Bloch, N., Aeschbach, S., Olbrich, H.M., Seifritz, E., Dürsteler-MacFarland, K.M., 2008. Psychobiological responses to drug cues before and after methadone intake in heroin-dependent patients: A pilot study. Eur. Neuropsychopharmacol. 18, 390–393. https://doi.org/10.1016/J.EURONEURO.2008.01.005.
Walter, M., Wiesbeck, G.A., Degen, B., Albrich, J., Oppel, M., Schulz, A., Schachinger, H., Dursteler-MacFarland, K.M., 2011. Heroin reduces startle and cortisol response in opioid-maintained heroin-dependent patients. Addict. Biol. 16, 145–151. https://doi.org/https://doi.org/10.1111/j.1369-1600.2010.00205.x.
Walter, M., Bentz, D., Schicktanz, N., Milnik, A., Aerni, A., Gerhards, C., Schwegler, K., Vogel, M., Blum, J., Schmid, O., Roozendaal, B., Lang, U.E., Borgwardt, S., de Quervain, D., 2015. Effects of cortisol administration on craving in heroin addicts. Transl. Psychiatry 5 e610–e610. https://doi.org/10.1038/tp.2015.101.
Wand, G.S., Dobs, A.S., 1991. Alterations in the hypothalamic-pituitary-adrenal axis in actively drinking alcoholics. J. Clin. Endocrinol. Metab. 72, 1290–1295. https://doi.org/10.1210/jcem-72-6-1290.
Wand, G.S., Oswald, L.M., McCaul, M.E., Wong, D.F., Johnson, E., Zhou, Y., Kuwabara, H., Kumar, A., 2007. Association of amphetamine-induced striatal dopamine release and cortisol responses to psychological stress. Neuropsychopharmacology 32, 2310–2320. https://doi.org/https://doi.org/10.1038/sj.npp.1301373.
Ward, A.S., Haney, M., Fischman, M.W., Foltin, R.W., 1997. Binge cocaine self-administration by humans: Smoked cocaine. Behav. Pharmacol. 8, 736–744. https://doi.org/10.1097/00008877-199712000-00009.
Watts, D.T., 1960. The Effect of Nicotine and Smoking on the Secretion of Epinephrine. Ann. N. Y. Acad. Sci. 90, 74–80. https://doi.org/10.1111/j.1749-6632.1960.tb32619.x.
Wemm, S., Fanean, A., Baker, A., Blough, E.R., Mewaldt, S., Bardi, M., 2013. Problematic drinking and physiological responses among female college students. Alcohol 47, 149–157.
White, T.L., Grover, V.K., de Wit, H., 2006. Cortisol effects of d-amphetamine relate to traits of fearlessness and aggression but not anxiety in healthy humans. Pharmacol. Biochem. Behav. 85, 123–131. https://doi.org/10.1016/j.pbb.2006.07.020.
Wilkins, J.N., Carlson, H.E., Van Vunakis, H., Hill, M.A., Gritz, E., Jarvik, M.E., 1982. Nicotine from cigarette smoking increases circulating levels of cortisol, growth hormone, and prolactin in male chronic smokers. Psychopharmacology (Berl) 78, 305–308. https://doi.org/10.1007/BF00433730.
Zimmermann, U., Spring, K., Wittchen, H.-U., Holsboer, F., 2004. Effects of ethanol administration and induction of anxiety-related affective states on the acoustic startle reflex in sons of alcohol-dependent fathers. Alcohol Clin. Exp. Res. 28, 424–432. https://doi.org/10.1097/01.ALC.0000117835.49673.CF.
Zis, A.P., Haskett, R.F., Ariav Albala, A., Carroll, B.J., 1984. Morphine inhibits cortisol and stimulates prolactin secretion in man. Psychoneuroendocrinology 9, 423–427. https://doi.org/10.1016/0306-4530(84)90050-7.
Zorick, T., Mandelkern, M.A., Lee, B., Wong, M.L., Miotto, K., Shahbazian, J., London, E.D., 2011. Elevated plasma prolactin in abstinent methamphetamine-dependent subjects. Am. J. Drug Alcohol Abuse 37, 62–67. https://doi.org/10.3109/00952990.2010.538945.
Zuurman, L., Roy, C., Schoemaker, R.C., Amatsaleh, A., Guimaeres, L., Pinquier, J.L., Cohen, A.F., Van Gerven, J.M.A., 2010. Inhibition of THC-induced effects on the central nervous system and heart rate by a novel CBi receptor antagonist AVE1625. J. Psychopharmacol. 24, 363–371. https://doi.org/10.1177/0269881108096509.