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Individual differences in the neuropsychopathology of addiction

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Drug addiction or substance-use disorder is a chronically relapsing disorder that progresses through binge/intoxication, withdrawal/negative affect, *and* preoccupation/anticipation *stages. These stages represent diverse neurobiological mechanisms that are differentially involved in the transition from recreational to compulsive drug use and from positive to negative reinforcement. The progression from recreational to compulsive substance use is associated with downregulation of the brain reward systems and upregulation of the brain stress systems. Individual differences in the neurobiological systems that underlie the processing of reward, incentive salience, habits, stress, pain, and executive function may explain (i) the vulnerability to substance-use disorder; (ii) the diversity of emotional, motivational, and cognitive profiles of individuals with substance-use disorders; and (iii) heterogeneous responses to cognitive and pharmacological treatments. Characterization of the neuropsychological mechanisms that underlie individual differences in addiction-like behaviors is the key to understanding the mechanisms of addiction and development of personalized pharmacotherapy.*

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Psychopathological framework

Three stages of the addiction cycle: binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation

Drug addiction is a chronically relapsing disorder that is characterized by compulsion to seek and take the drug, loss of control in limiting drug intake, and emergence of a negative emotional state, reflecting a motivational withdrawal syndrome, when access to the drug is prevented.[1] Drug addiction includes three stages: *preoccupation/anticipation*, *binge/intoxication*, and *withdrawal/negative affect*. These three stages feed into each other to produce an addiction cycle. Each stage becomes more intense after each cycle, leading to the pathological state of addiction. These three stages reflect incentive salience/pathological habits, reward deficits/stress surfeit, and executive function deficits, respectively, which provide a powerful impetus for compulsive drug-seeking behavior that is associated with drug addiction. These domains of dysfunction corre-

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spond to neuroadaptations that reflect allostatic changes in three key neurocircuits that mediate compulsive drug seeking: basal ganglia, extended amygdala, and prefrontal cortex, respectively (*Figure 1A*).[2] Allostasis in the context of addiction is the process by which the body responds to challenges to maintain apparent homeostasis through changes in brain reward and stress mechanisms.[3] The allostatic state represents a chronic deviation of reward set point that is mostly observed during abstinence and not observed when the individual is actively taking drug. Thus, the allostatic view extends counteradaptive theory by stating that not only does the *b-process* get larger with chronic drug use but the reward set point also progressively shifts downward, thus creating an allostatic state (*Figure 1B*).[3,4] This model has been proposed to explain the persistent changes in motivation in drug-dependent individuals. We propose that the relative contribution of each of these three stages to drug use and drug addiction varies both between and within individuals across time.

From positive to negative reinforcement

Another level of complexity that is added to these three stages is the fact that drug addiction includes a transition from impulsive to compulsive behaviors and from positive to negative reinforcement (*Figure 2*).[5,6] Impulsivity is

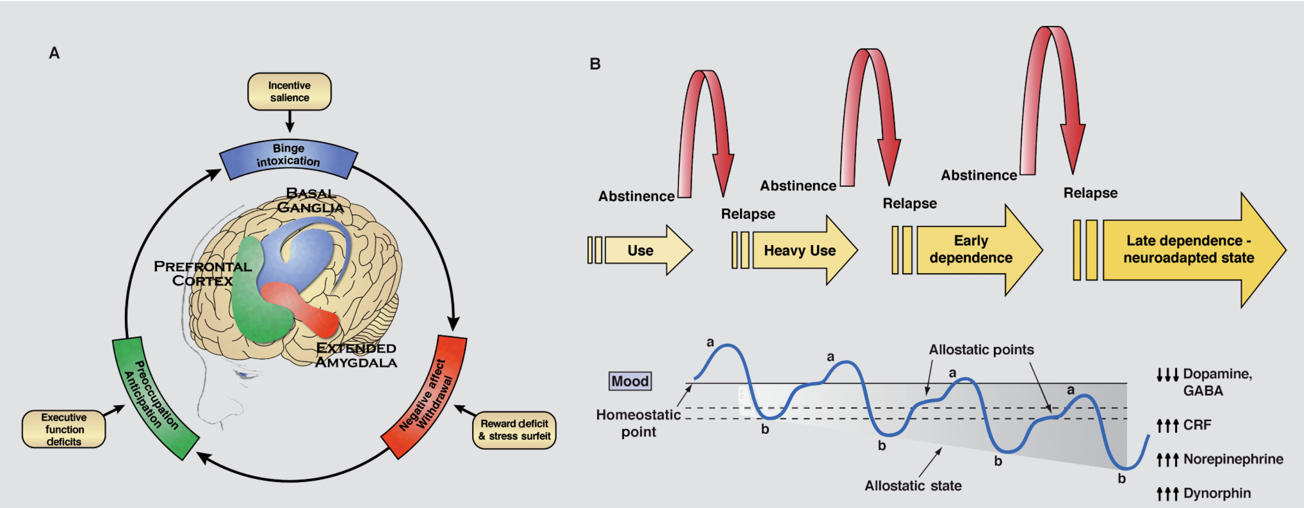


Figure 1. (Left) Three stages of the addiction cycle: *binge/intoxication*, *withdrawal/negative affect*, and *preoccupation/anticipation*. These three stages reflect incentive salience/pathological habits, reward deficits/stress surfeit, and executive function deficits, respectively, to provide a powerful impetus for compulsive drug-seeking behavior associated with drug addiction. These domains of dysfunction correspond to neuroadaptations that reflect allostatic changes in three key neurocircuits to mediate compulsive drug seeking: basal ganglia, extended amygdala, and prefrontal cortex, respectively. **(Top right)** The progression of alcohol dependence over time. The schematic illustrates the shift in underlying motivational mechanisms. From initial, positively reinforcing, pleasurable alcohol effects, the addictive process progresses over time to being maintained by negatively reinforcing relief from a negative emotional state. **(Bottom right)** The *a-process* represents a positive hedonic or positive mood state, and the *b-process* represents a negative hedonic or negative mood state. The affective stimulus (state) has been argued to be the sum of both the *a-process* and *b-process*. An individual who experiences a positive hedonic mood state from a drug of abuse with sufficient time between readministering the drug is hypothesized to retain the *a-process*. An appropriate counteradaptive opponent process (*b-process*) that balances the activational process (*a-process*) does not lead to an allostatic state. Changes in the affective stimulus (state) in an individual with repeated frequent drug use may represent a transition to an allostatic state in the brain reward systems and, by extrapolation, a transition to addiction. Notice that the apparent b-process never returns to the original homeostatic level before drug taking begins again, thus creating a progressively greater allostatic state in the brain reward system. The counteradaptive opponent-process (*b-process*) does not balance the activational process (*a-process*) but in fact shows residual hysteresis. Although these changes that are illustrated in the figure are exaggerated and condensed over time, the hypothesis is that even during post-detoxification (a period of protracted abstinence), the reward system still bears allostatic changes. The following definitions apply: *allostasis*, the process of achieving stability through change; *allostatic state*, a state of chronic deviation of the regulatory system from its normal (homeostatic) operating level; *allostatic load*, the cost to the brain and body of the deviation, accumulating over time, and reflecting in many cases pathological states and accumulation of damage.

Bottom right panel from reference 3: Koob GF, Le Moal M. Drug addiction, dysregulation of reward, and allostasis. *Neuropsychopharmacology*. 2001;24(2):97-129. Copyright © Nature Publishing Group, 2001. Top right panel from reference 4: Heilig M, Koob GF. A key role for corticotropin-releasing factor in alcohol dependence. *Trends Neurosci*. 2007;30(8):399-406. Copyright © Elsevier Applied Science Publishing, 2007 defined as "a predisposition toward rapid, unplanned reactions to internal or external stimuli without regard for the negative consequences of these reactions to [themselves] or others."[7] Compulsivity is defined as "perseverative, repetitive actions that are excessive and inappropriate."[8] Positive reinforcement is defined as the process by which presentation of a stimulus increases the probability of a response. Negative reinforcement is defined as the process by which removal of an aversive stimulus (or aversive state in the case of addiction) increases the probability of a response.[9] Impulsivity often dominates at the early stages of drug addiction through repeated binge/intoxication and positive reinforcement. Individuals seek and take the drug for its initial pleasurable and reinforcing effects without regard for the potential future negative consequences of using drugs. Compulsivity dominates at later stages of drug addiction through the emergence of negative emotional states in the *withdrawal/negative affect* stage and anticipation of obtaining the drug in the *preoccupation/anticipation* stage. Such compulsivity leads to the escalation of drug intake and perseverative drug use despite adverse consequences. The transition from positive to negative reinforcement reflects a change in the underlying psychological and neurobiological mechanisms of motivation (*Figure 2*). Motivation can be defined as a "tendency of the whole animal to produce organized activity."[10] The neural substrates for the two sources of reinforcement that play a key role in allostatic neuroadaptations derive from two key motivational systems that are required for survival: brain reward system and brain stress system.

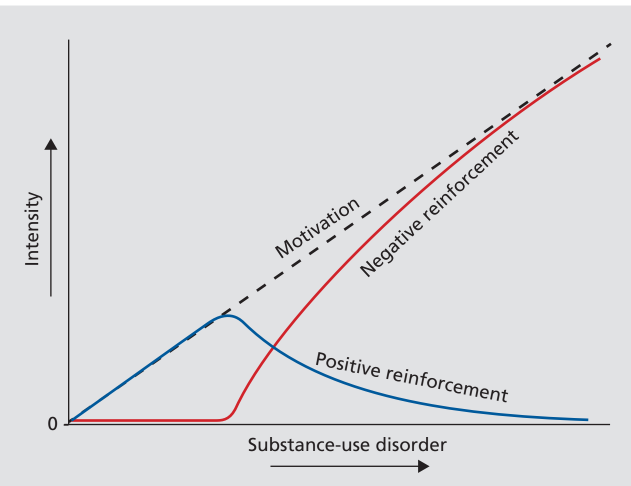


Figure 2. Schematic of the progression of drug addiction over time, illustrating the shift in underlying motivational mechanisms. From initial, positive reinforcing, pleasurable drug effects, the addictive process progresses over time to being maintained by negative-reinforcing relief from a negative emotional state. Adapted from reference 6: Koob GF. Theoretical frameworks and mechanistic aspects of alcohol addiction: alcohol addiction: alcohol addiction as a reward deficit disorder. In: Sommer WH, Spanagel R, eds. *Behavioral Neurobiology of Alcohol Addiction*. Berlin, Germany: Springer-Verlag; 2013:3-30. Current Topics in Behavioral Neuroscience; vol 13. © 2011, Springer-Verlag Berlin Heidelberg

Within the addiction process, the concept of motivation is linked to hedonic, affective, and emotional states in the context of temporal dynamics that are elaborated by Solomon's opponent process theory of motivation.[11] Hedonic, affective, or emotional states, once initiated, are modulated by the central nervous system with mechanisms that reduce the intensity of hedonic feelings. This theory postulates that any motivational stimulus activates two opposing motivational processes. The *a-process* consists of positive or negative hedonic responses, has a fast onset and offset, correlates with the intensity, quality, and duration of the stimulus, and shows tolerance. The *b-process* appears after the *a-process* has terminated, is opposite in direction, is sluggish in onset, is slow to build up and decay, and gets larger with repeated exposure. The initial acute effect of a drug of abuse (ie, the *a-process* or positive hedonic response) was hypothesized to be opposed or counteracted by the *b-process* as homeostatic changes in brain systems. With repeated exposure to drugs, the *b-process* sensitizes, appears earlier after the unconditioned stimulus, lasts longer, and masks the *a-process*, leading to apparent tolerance.[12] Two types of biological processes have been proposed to describe the mechanisms that underlie the neuroadaptations that are associated with generation of the opponent process in drug addiction: within-system adaptation and between-system adaptation.[13] In the within-system process, the drug elicits an opposing, neutralizing reaction within the same system in which the drug elicits its primary and unconditioned reinforcing actions. In the between-system process, neurobiological systems are recruited that are different from the ones that were initially activated by the drug.

Neurobiological mechanisms of drug addiction

Binge/intoxication stage

Intense research efforts over the past three decades have been dedicated to revealing the neurochemical elements and neuronal networks that are responsible for the *binge/intoxication* stage (*Figure 3*).[14] Converging evidence suggests that three main contributors to the *binge/intoxication* stage in the early stages of drug addiction are (i) the acute positive hedonic value of drugs,[15] (ii) sensitization of incentive salience,[16] and (iii) inherent poor cognitive insight.[17] The later stages of drug addiction also exhibit a *binge/intoxication* stage that also includes tolerance and is fueled by the negative emotional states that are an important driving force to the maintenance of chronic and heavy drug use.

Intoxicating doses of drugs, including alcohol, produce the release of dopamine and endogenous opioids in the ventral striatum that correlate with the subjective effects of drugs, including feelings of being "high."[18,19] Earlier preclinical work showed that all drugs of abuse increase dopamine release in the ventral striatum, leading to theories that suggested that this increase may be related to the hedonic value of drugs of abuse.[15] Moreover, dopamine plays a key role in psychostimulant reward, but dopamine-independent reward has also been demonstrated for opioids and alcohol.[20-22] Further work established a key common role for dopamine in addiction. The dopaminergic system is important within a subcomponent of motivational systems that allows the attribution of incentive salience. Incentive salience (anchored within the construct of conditioned reinforcement) is a phenomenon by which a previously neutral stimulus acquires incentive value through pairing with a drug of abuse.[16] Robust evidence indicates that dopamine plays a minor role, if any, in reward processing per se and may represent instead a reward prediction error signal.[23]

The theory of sensitization of incentive salience has its origins in early work on conditioned reinforcement.[24] Prominent work has shown that dopamine neurons are crucial for mediating such conditioned reinforcement. Dopamine neurons in the ventral tegmental area and substantia nigra have been shown to exhibit phasic responding to a nonpredicted reward. After repeated exposure, the same neurons stop responding to a predictable reward and instead start responding to the earliest cue that predicts the future reward.[25,26] This process allows neutral cues to acquire incentive salience and thus elicit behavioral approach. One hypothesis is that the progressive sensitization of this phasic responding to cues that is associated with drug reward may contribute to maladaptive craving that is observed in individuals with substance-use disorders,[27,28] although clinical evidence for such a phenomenon is sparse.[29] Preclinical evidence indicates that drugs of abuse can produce a shift in the excitatory balance of dopamine neurons after acute administration,[30-38] suggesting that neuroadaptations in the dopamine incentive salience system can occur early in the addiction process. Moreover, a recent study in humans showed that the phenomenon of conditioned responding of dopamine neurons to drug-predictive cues occurred in recreational cocaine users who did not meet the criteria for cocaine-use disorders.[39] These results suggest that the phenomenon of sensitization of incentive salience may be important early in the addiction process but may not be a key mechanism in later stages of addiction. In contrast, there is converging evidence in the preclinical literature that the later stages of addiction may instead involve a transition from goal-directed behavior that is mediated by the ventral striatum to habit behavior that is under the control of the dorsal striatum and that is facilitated by chronic exposure to the drug.[40-49]

Preclinical work has shown that the activation of dopamine D_1 but not D_2 receptors,[50,51] μ-opioid receptors (MORs),[52] nociceptin opioid (NOP) receptors,[53] and α4-, β2-, and α6-containing nicotinic acetylcholine receptors (nAChRs) are required for the acute rewarding and reinforcing effects of drugs. However, these requirements are usually specific to the particular drug of abuse (D_1 for cocaine, MOR for opioids, and nAChRs for nicotine). The only exception may be NOP receptors, which have recently been shown to affect cocaine, heroin, and alcohol self-administration and drug-induced conditioned place preference.[53] Other neurotransmitter systems, including the serotonin 5-hydroxytryptamine (5-HT),[54,55] γ-aminobutyric acid (GABA),[55] acetylcholinergic (ACh),[55] and endocannabinoid[35,56-59] systems, are believed to contribute to the *binge/intoxication* stage by modulating dopamine, opioid, and nicotinic systems, although a more central role for the GABA system has been identified in the mediation of the intoxicating and reinforcing effects of alcohol.[60]

Withdrawal/negative affect stage

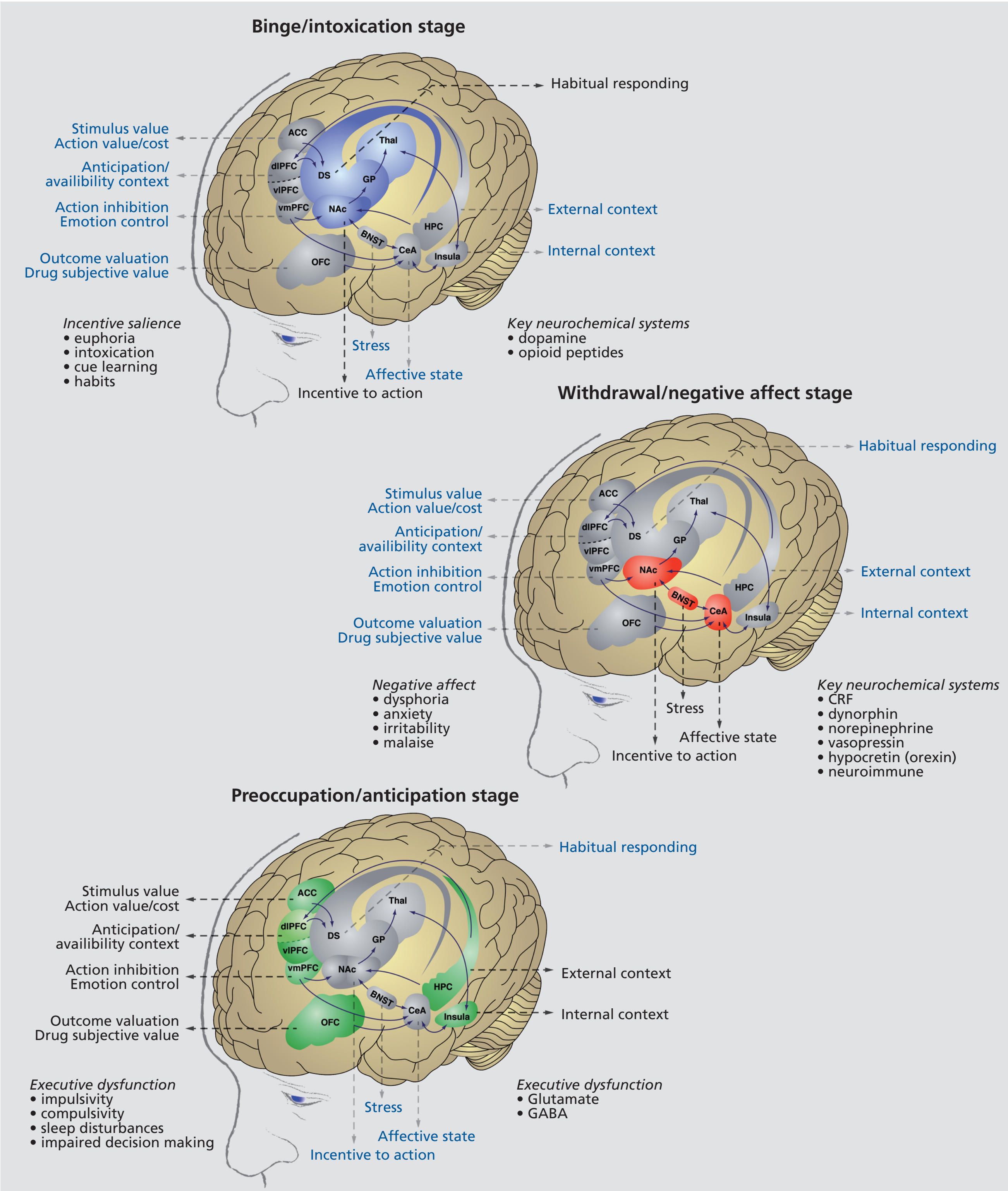
Our understanding of the neurobiology of the *withdrawal/negative affect* stage has dramatically increased in the past decade. This stage includes different sources of motivation to take drugs, including chronic irritability, emotional pain, malaise, dysphoria, alexithymia (in-ability to identify/express emotions), states of stress, and the loss of motivation for natural rewards. For example, chronic administration of all major drugs of abuse leads to stress and anxiety-like responses during acute and protracted abstinence.[61]

One explanation for the blunted function of the reward system during abstinence involves within-system neuroadaptations, in which the primary target of the drug rapidly adapts to neutralize the effect of the drug. Long-lasting within-system adaptations can then lead to a decrease in brain reward function when the drug is removed.[13] For example, cocaine acutely produces dopamine and serotonin release, but decreases in dopaminergic and serotonergic transmission have been observed in the ventral striatum during cocaine withdrawal in rats.[62] Even more compelling are studies in humans that reported lower self-reported rewarding effects of drugs and a lower striatal dopamine response after amphetamine/methylphenidate challenges in active and detoxified abusers than in controls.[63-66] Similar neuroadaptations are hypothesized to occur for other classes of drugs, including increases in MOR responsivity during opioid withdrawal,[67,68] decreases in GABAergic transmission in the ventral striatum, and increases in *N*-methyl-D-aspartate glutamatergic transmission in the ventral striatum.[69,70] Complex regional changes in function in key brain regions, including the ventral tegmental area, ventral striatum, interpeduncular nucleus (IPN), amygdala, and habenula, have been reported for nicotine and alcohol addiction, among other addictions.[71,72] Such within-system neuroadaptations may contribute to the *withdrawal/negative affect stage* by decreasing brain reward function during abstinence but may also be involved in the *preoccupation/anticipation* stage by providing a greater hedonic driving force to resume drug use.

Another explanation for the lower function of the reward system during abstinence involves between-system neuroadaptations, in which systems other than those that are involved in the positive rewarding effects of drugs are recruited or dysregulated by chronic drug use to oppose the rewarding effects of drugs of abuse.[13] A central component of this between-system neuroadaptation is activation of the stress pathways, including the hypothalamic-pituitary-adrenal (HPA) axis and extrahypothalamic brain stress systems that are mediated by corticotropin-releasing factor (CRF), norepinephrine, and dynorphin.[73-75] Withdrawal from drugs of abuse acutely increases adrenocorticotropic hormone, corticosterone, and extended amygdala CRF and dynorphin during withdrawal.[76-83]

Two main brain circuits probably contribute to these opponent-like processes that lower brain reward function and increase brain stress system function. Both of these circuits are heavy influenced by CRF. One circuit involves the extended amygdala, which encompasses the central nucleus of the amygdala (CeA), bed nucleus of the stria terminalis (BNST), and part of the nucleus accumbens (*Figure 3*). The extended amygdala integrates brain arousal-stress and reward system information[84] to produce the between-system opponent process that is elaborated above. The CRF system in the extended amygdala is activated during acute withdrawal from cocaine, alcohol, opioids, Δ^9-tetrahydrocannabinol, and nicotine.[78,85,86] Similar effects have been observed with alcohol in the lateral BNST.[81] Cocaine withdrawal produces anxiety-like responses that can be reversed by a CRF-receptor antagonist.[87,88] Similar results have been observed with nicotine,[86,89,90] alcohol,[79,91] and opioids.[88,92,93] Moreover, the ability of CRF receptor antagonists to block the anxiogenic-like and aversive-like motivational effects of drug withdrawal predicts the efficacy in reducing compulsive-like self-administration of cocaine,[94] nicotine,[86] and heroin[95] in rats. Although very promising, the clinical development of CRF_1-receptor antagonists for the treatment of drug- and alcohol-use disorders has mostly failed.[96,97] However, these failures should be considered cautiously because the compounds that have been used have less than ideal pharmacokinetics/pharmacodynamics and physicochemical properties, and several other shortcomings in these studies may explain their negative outcomes (for details, see Spierling and Zorrilla[98]).

The excessive release of dopamine and opioid peptides produces subsequent activation of the dynorphin system in the basal ganglia and extended amygdala, which has been hypothesized to feed back to decrease dopamine release and contribute to the dysphoric syndrome that is associated with cocaine dependence.[99] Dynorphins produce aversive dysphoric-like effects in animals and humans and have been hypothesized to mediate negative emotional states[100,101] and depression-like, aversive responses to stress and dysphoric-like responses during withdrawal from drugs of abuse. Recent evidence suggests that the dynorphin/κ-opioid system in the extended amygdala also mediates compulsive-


Binge/intoxication stage
Habitual responding
Stimulus value
Action value/cost
Anticipation/
availibility context
Action inhibition
Emotion control
Outcome valuation
Drug subjective value
External context
Internal context
ACC
Thal
dlPFC
DS
GP
vlPFC
vmPFC
NAc
BNST
HPC
CeA
Insula
OFC
Incentive salience
• euphoria
• intoxication
• cue learning
• habits
Stress
Affective state
Incentive to action
Key neurochemical systems
• dopamine
• opioid peptides
Withdrawal/negative affect stage
Habitual responding
Stimulus value
Action value/cost
Anticipation/
availibility context
Action inhibition
Emotion control
Outcome valuation
Drug subjective value
External context
Internal context
ACC
Thal
dlPFC
DS
GP
vlPFC
vmPFC
NAc
HPC
BNST
CeA
Insula
OFC
Negative affect
• dysphoria
• anxiety
• irritability
• malaise
Stress
Affective state
Incentive to action
Key neurochemical systems
• CRF
• dynorphin
• norepinephrine
• vasopressin
• hypocretin (orexin)
• neuroimmune
Preoccupation/anticipation stage
Habitual responding
Stimulus value
Action value/cost
Anticipation/
availibility context
Action inhibition
Emotion control
Outcome valuation
Drug subjective value
External context
Internal context
ACC
Thal
dlPFC
DS
GP
vlPFC
vmPFC
NAc
HPC
BNST
CeA
Insula
OFC
Executive dysfunction
• impulsivity
• compulsivity
• sleep disturbances
• impaired decision making
Stress
Affective state
Incentive to action
Executive dysfunction
• Glutamate
• GABA

like responding for methamphetamine, heroin, and alcohol with extended access and dependence.[101]

Another system is the habenula-to-IPN pathway. The habenula plays a key role in encoding aversive states,[102,103] in part by decreasing dopamine neuron firing in the ventral tegmental area after failure to receive an expected reward.[102,103] This hypothesis is consistent with the finding that nAChRs in the habenula-IPN appear to modulate aversive responses to nicotine[104] and nicotine withdrawal.[105,106] We recently reported that the habenula-IPN pathway is also under the influence of the CRF system.[90,106] Activation of this pathway during nicotine withdrawal was potentiated by CRF-producing neurons in the ventral tegmental area that project to the IPN. The downregulation of CRF messenger RNA in the ventral tegmental area and CRF_1-receptor blockade in the IPN prevented emergence of the negative emotional states associated with withdrawal and reduced excessive nicotine intake after abstinence.[90,106]

In addition to these subcortical circuits that involve the brain reward and stress systems, the insular cortex is an important cortical region for emotional aspects of the *withdrawal/negative affect* stage. Cravings for food, cocaine, and nicotine have been shown to activate the insular cortex,[107-109] and tobacco smokers with damage to the insular cortex were able to stop smoking easily with little, if any, withdrawal symptoms, craving, or relapse.[110] The insula is hypothesized to integrate autonomic, visceral, and emotional information[111] during withdrawal and abstinence to produce the motivation to obtain the drug within a negative reinforcement framework (ie, obtain relief from negative emotional states associated with withdrawal). Supporting this hypothesis, imaging studies have reported differential activation of the insula during craving, possibly reflecting interoceptive cues. Such activation during craving also could be driven by the activation of cortical CRF systems when considering the substantial level of CRF neurons and CRF_1 receptors in the insula.[112,113] Finally, reactivity of the insular cortex has been suggested to serve as a biomarker to help predict relapse.[114]

Preoccupation/anticipation stage

Intoxicating doses of drugs, particularly alcohol, marijuana, and opioids, and high doses of psychostimulants are associated with cognitive impairments, including poor working memory, inattention, impulsivity, and delay discounting[115] (for review, see Oscar-Berman and Hutner[116]). Such cognitive impairment significantly contributes to relapse and the escalation of drug intake and results from drug-induced dysfunction of the dorsolateral, ventrolateral, and lateral prefrontal cortex and orbitofrontal cortex (*Figure 3*).[115,117-120] For example, working-memory impairments have been associated with higher levels of alcohol, methamphetamine, and cocaine use in both humans and rats.[121-125]

Craving is a key part of the *preoccupation/anticipation* stage. Large interindividual variability has been observed in the intensity of craving and the source of craving. In humans, cue-induced craving activates the dorsolateral prefrontal cortex, anterior cingulate gyrus, and medial orbitofrontal cortex.[126-130] Cues that are associated with cocaine craving also increase do-

Figure 3. (Opposite) Neural circuitry associated with the three stages of the addiction cycle. (**A**) *Binge/intoxication* stage. Reinforcing effects of drugs may engage associative mechanisms and reward neurotransmitters in the nucleus accumbens shell and core and then engage stimulus-response habits that depend on the dorsal striatum. Two major neurotransmitters that mediate the rewarding effects of drugs of abuse are dopamine and opioid peptides. (**B**) *Withdrawal/negative affect* stage. The negative emotional state of withdrawal may engage the activation of the extended amygdala. The extended amygdala is composed of several basal forebrain structures, including the bed nucleus of the stria terminalis, central nucleus of the amygdala, and possibly a transition area in the medial portion (or shell) of the nucleus accumbens. Major neurotransmitters in the extended amygdala that are hypothesized to play a role in negative reinforcement are corticotropin-releasing factor, norepinephrine, and dynorphin. The extended amygdala has major projections to the hypothalamus and brain stem. (**C**) *Preoccupation/anticipation* (craving) stage. This stage involves the processing of conditioned reinforcement in the basolateral amygdala and processing of contextual information in the hippocampus. Executive control depends on the prefrontal cortex and includes the representation of contingencies, the representation of outcomes, their value, and subjective states (ie, craving and, presumably, feelings) associated with drugs. The subjective effects, termed drug craving in humans, involves activation of the orbitofrontal and anterior cingulate cortex and temporal lobe, including the amygdala, in functional imaging studies. A major neurotransmitter that is involved in the craving stage is glutamate that is localized in pathways from frontal regions and the basolateral amygdala that project to the ventral striatum. ACC, anterior cingulate cortex; BNST, bed nucleus of the stria terminalis; CeA, central nucleus of the amygdala; CRF, corticotropin-releasing factor; dlPFC, dorsolateral prefrontal cortex; DS, dorsal striatum; GABA, γ-aminobutyric acid; GP, globus pallidus; HPC, hippocampus; NAc, nucleus accumbens; OFC, orbitofrontal cortex; Thal, thalamus; vlPFC, ventrolateral prefrontal cortex; vmPFC, ventromedial prefrontal cortex.

Modified with permission from reference 14: Koob GF, Everitt BJ, Robbins TW. Reward, motivation, and addiction. In: Squire LG, Berg D, Bloom FE, Du Lac S, Ghosh A, Spitzer N, eds. *Fundamental Neuroscience*. 3rd edition. Amsterdam, the Netherlands: Academic Press; 2008:987-1016.

pamine release in the ventral striatum, prefrontal cortex, and amygdala and endogenous opioid peptide release in the frontal cortex and anterior cingulate.[131-134] Such activation of the reward/salience systems during acute craving episodes is further potentiated because of a decrease in the inhibitory function of the prefrontal cortex (orbitofrontal cortex, ventromedial cortex, and anterior cingulate cortex) in humans with substance-use disorders.[19,135,136] Indeed, substance-use disorder is associated with chronic executive dysfunction, including impairments in decision making, self-regulation, inhibitory control, attention, and working memory,[117] that may be caused by increases in GABAergic and CRF activity in the prefrontal cortex.[123,137] Another key neurotransmitter system that is associated with impairments in behavioral inhibition is the dopaminergic system. Brain imaging has consistently shown lower dopamine D_2 receptor availability in the striatum and prefrontal cortex after protracted abstinence in humans, nonhuman primates, and rodents.[138] Preclinical models have shown that lower D_2 receptor availability is associated with greater motivation for cocaine[139] and cognitive deficits.[140] Decreases in striatal dopamine, combined with increases in GABA and CRF signaling in the prefrontal cortex, may lead to an overactive "Go" system that drives craving and habits and a hypoactive "Stop" system that normally inhibits impulsive behavior and negative emotional states through the activation of specific corticostriatal loops.[141-144]

Implications for personalized medicine

Our thesis is that there are considerable individual differences in the patterns of drug use and the psychological mechanisms that drive drug use. Drug use may be driven by the *binge/intoxication* stage for some individuals and by the *withdrawal/negative affect* stage for others. With psychostimulants and even alcohol, binge-like patterns can predominate in some individuals. Such individuals may escalate their drug intake in a binge-like pattern for various reasons, including peer pressure, sensation seeking, externalizing disorders, and drug-induced cognitive impairment (eg, decision making, monitoring, renegade attention, and transcendence failure) with little, if any, initial negative emotional symptoms. Other individuals may quickly develop a pattern of chronic and heavy use that is caused by either conscious or unconscious attempts to self-medicate existing negative emotional states. Such individuals often have preexisting conditions that generate powerful negative emotional states, such as posttraumatic stress disorders, sexual abuse, major depressive disorder, or anxiety disorder, and will use drugs to obtain relief from these negative emotional states. However, chronic high-dose binge-like patterns of drug intake can cause the development of negative emotional states and ultimately drive self-medication of a state that is created by the drug itself. Ultimately, both the *binge/intoxication* stage and *withdrawal/negative affect* stage will contribute to a pathological state of compulsive drug seeking and taking. One intriguing area of research is the identification of genetic, biological, and psychological subpopulations of humans with substance-use disorder within the framework of the three stages of addiction to better understand the drug addiction process and potentially predict treatment efficacy. Our thesis is that addiction treatments may benefit from the development of medications that specifically target each phase of the addiction process to personalize treatment and obtain better treatment outcome and compliance. In the past decade, notable advances have been made, and there is clear clinical evidence in humans that some treatments (eg, naltrexone) may be better suited for the treatment of the *binge/intoxication* stage, whereas others (eg, acamprosate) may be more appropriate for the *preoccupation/anticipation* stage. However, to date, these findings have had little impact in real life for the treatment of substance-use disorders because of the limited number of available medications and limited number of patients who receive appropriate treatment.

There are individual differences in executive function, prefrontal cortex function, brain stress system function, and dopamine reward signaling, and the genetics of negative emotional states may help identify subgroups of patients with substance-use disorder that may help predict treatment outcome. Attempts are being made to identify genetic markers, including single-nucleotide polymorphisms (SNPs), that may predict the vulnerability to substance-use disorders and responsiveness to treatment. Several research groups have identified gene variants in the metabolic enzymes and receptors that are directly modulated by drugs of abuse, such as MOR, nAChRs, cytochrome p450, and alcohol dehydrogenase. Such findings are very encouraging and suggest that some of these gene variants may predict the response to specific treatments.[145-149] Several SNPs that are associated with the CRF system have also been associated with excessive alcohol use. An association was found between SNPs that are related to the CRF_1 receptor gene (*Crhr1*) and binge drinking in adolescents and alcohol-dependent adults.[150-152] Another important genetic association has been found between alcohol dependence and SNPs that are related to the gene that encodes neuropeptide Y (NPY). NPY is an anxiolytic peptide that is involved in emotional regulation and stress coping and is known to antagonize the effects of CRF on addiction-like behaviors. Studies have linked SNPs of the Y_2 receptor gene (*NPY2R*) and alcohol dependence, alcohol withdrawal symptoms, comorbid alcohol and cocaine dependence, and cocaine dependence.[153] The G1258A polymorphism of the NPY gene has been linked to alcohol dependence.[154] The rs16147 SNP of the NPY promoter gene was linked to tobacco addiction.[155] Should a medication become available that modulates CRF or NPY, such genetic analysis may reveal that subpopulations of subjects who carry specific SNPs might be more responsive than others.

Conclusions

Drug addiction is a chronically relapsing disorder that is associated with compulsive drug seeking and taking that progress through the *binge/intoxication*, *withdrawal/negative affect*, and *preoccupation/anticipation* stages. These three stages have diverse neurobiological mechanisms that are involved in the transition from recreational to compulsive drug use. We hypothesize that individual differences in the neurobiological systems that underlie the processing of reward, incentive salience, stress, pain, habits, and executive function may explain (i) the vulnerability to developing a substance-use disorder; (ii) the diversity of emotional, motivational, and cognitive profiles of individuals with substance-use disorders; and (iii) the heterogeneous responses to cognitive and pharmacological treatments. We propose that characterization of the neuropsychological mechanisms that underlie individual differences in addiction-like behaviors is a key to understanding the mechanisms of addiction and development of personalized medicine through genomic medicine and personalized pharmacotherapy. ❑

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Diferencias individuales en la neuropsicopatología de la adicción

La adicción a drogas o el trastorno por uso de sustancias es un trastorno crónico con recaídas que progresa a través de las etapas de compulsión / intoxicación, abstinencia/afecto negativo y preocupación/anticipación. Estas etapas representan diversos mecanismos neurobiológicos que participan diferenciadamente en la transición desde el uso recreacional al uso compulsivo de la droga y desde un refuerzo positivo a uno negativo. La progresión, desde un uso recreacional de la sustancia a uno compulsivo, está asociada con una regulación negativa de los sistemas cerebrales de recompensa y una regulación positiva de los sistemas cerebrales del estrés. Las diferencias individuales en los sistemas neurobiológicos que están a la base del procesamiento de la recompensa, del aumento del incentivo, de los hábitos, del estrés, del dolor, y de la función ejecutiva pueden explicar: 1) la vulnerabilidad al trastorno por uso de sustancias, 2) la diversidad de los perfiles emocionales, motivacionales y cognitivos de los sujetos con trastornos por uso de sustancias y 3) las respuestas heterogéneas a los tratamientos cognitivos y farmacológicos. La clave para comprender los mecanismos de la adicción y el desarrollo de una farmacoterapia personalizada es la caracterización de los mecanismos neuropsicológicos que subyacen a las diferencias individuales en las conductas adictivas.

Différences individuelles dans la neuro-psychopathologie de l'addiction

L'addiction aux drogues ou le trouble de l'usage d'une substance est une maladie à rechutes chroniques qui évolue par des étapes de compulsion/intoxication, sevrage/effet négatif et préoccupation/anticipation. Ces étapes représentent des mécanismes neurobiologiques variés différemment impliqués dans la transition allant de l'usage récréatif à l'usage compulsif d'une drogue et du renforcement positif au renforcement négatif. Le passage de l'usage récréatif à l'usage compulsif d'une substance est associé à une régulation négative des systèmes cérébraux de récompense et à une régulation positive des systèmes cérébraux de stress. Des différences individuelles dans les systèmes neurobiologiques sous-tendant le processus de récompense, de saillance incitative, d'habitudes, de stress, de douleur et de fonction exécutive peuvent expliquer 1) la vulnérabilité aux troubles liés à l'usage de substances ; 2) la diversité des profils émotionnels, motivationnels et cognitifs des individus souffrant de troubles liés à l'usage de substances et 3) les réponses hétérogènes aux traitements cognitifs et pharmacologiques. La clé de la compréhension des mécanismes d'addiction et du développement de traitements pharmacologiques personnalisés est la caractérisation des mécanismes neuropsychologiques sous-tendant les différences individuelles dans les comportements addictifs.