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Individual Differences in Prefrontal Cortex Function and the Transition from Drug Use to Drug Dependence

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Abstract

Several neuropsychological hypotheses have been formulated to explain the transition to addiction, including hedonic allostasis, incentive salience, and the development of habits. A key feature of addiction that remains to be explored is the important individual variability observed in the propensity to self-administer drugs, the sensitivity to drug-associated cues, the severity of the withdrawal state, and the ability to quit. In this review, we suggest that the concept of self-regulation, combined with the concept of modularity of cognitive function, may aid in the understanding of the neural basis of individual differences in the vulnerability to drugs and the transition to addiction. The thesis of this review is that drug addiction involves a failure of the different subcomponents of the executive systems controlling key cognitive modules that process reward, pain, stress, emotion, habits, and decision-making. A subhypothesis is that the different patterns of drug addiction and individual differences in the transition to addiction may emerge from differential vulnerability in one or more of the subcomponents.

Keywords

Stress; module; individual differences; cognitive; prefrontal; loss of control; emotion; pain; reward; incentive salience; habits

Background

Addiction

Drug addiction is a chronic relapsing disorder characterized by increased motivation to seek drugs and is characterized in the human condition by increased drug intake, loss of control over drug intake, and compulsive drug taking and drug seeking. Three major components of the addiction cycle have been identified—*binge/intoxication*, *withdrawal/negative affect*, and *preoccupation/anticipation* (craving)—and incorporate the constructs of impulsivity and compulsivity with varying contributions of positive and negative reinforcement (Koob and Le Moal, 2008; Koob et al., 2008). From a theoretical perspective, the increased motivation to seek drugs has been hypothesized to involve counteradaptive mechanisms (Solomon and Corbit, 1974; Wikler, 1973), increases in incentive salience (Robinson and Berridge, 1993),

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or a combination of both constructs in the form of an allostatic change in hedonic set point (Ahmed and Koob, 1998; Koob and Le Moal, 1997, 2001).

The counteradaptive theory states that two opposing processes control affect and the motivational changes observed after chronic drug use. The initial rewarding effect of the drug (*a-process*) will trigger a delayed aversive effect (*b-process*) that gets larger with chronic drug use and will counteract the *a-process* to maintain homeostasis. This model has been proposed to explain tolerance, withdrawal, and the aversive craving state observed during abstinence (Solomon and Corbit, 1974; Laulin et al., 1999). Allostasis, in the context of addiction, is the process of maintaining apparent reward function stability through changes in brain reward and stress mechanisms (Koob and Le Moal, 2001). 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 the *b-process* gets larger with chronic drug use but the reward set point from which the *a-process* and *b-process* are anchored progressively shifts downward, creating an allostatic state. This model has been proposed to explain the persistent changes in motivation in drug-dependent individuals.

Although drug addiction is often viewed as one disorder, it is important to note that different drugs produce different patterns of addiction that engage different components of the addiction cycle (Koob et al., 2008). Opioid and alcohol addictions are characterized by an intense *withdrawal/negative affect* stage with profound dysphoria and physical and emotional pain often followed by intoxication during the *binge/intoxication* stage, thus representing one of the main driving forces for compulsive drug seeking and drug taking. Profound tolerance occurs to the intoxication associated with alcohol and opioids, but some intoxication always remains. Nicotine addiction is not associated with major intoxication but is instead characterized by highly compulsive titrated intake of the drug to the point that daily activities (e.g., social contact, meals, and sleep) are perturbed and constrained by the patterns of nicotine intake. Nicotine addiction is also associated with intense dysphoria, irritability, sleep disturbances, and craving during abstinence. Marijuana addiction shares aspects of both opioid and nicotine addiction, with an initial intense *binge/intoxication* stage that progressively transitions to regular and titrated marijuana intake during the day and dysphoria during abstinence. Cocaine and amphetamine addiction are characterized by major *binge/intoxication* and *preoccupation/anticipation* stages, with an intense craving for the drug and binges that can last hours or days and are usually followed by intense dysphoria during acute withdrawal and protracted abstinence associated with anxiety, dysphoria, and intense craving. Again, profound tolerance develops to the intoxication associated with the drug during a binge.

Important individual differences in the different stages of addiction, as well as in the vulnerability to the transition to addiction, have been observed in humans and animals (Anthony et al., 1994; Crowley et al., 1998; de Wit et al., 1986; Deroche-Gamonet et al., 2004). Significant individual differences have been observed in (*i*) the sensitivity to the pharmacological effects of the drug, (*ii*) the propensity to self-administer the drug, (*iii*) resistance to extinction, (*iv*) sensitivity to drug-associated cues, (*v*) relapse, and (*vi*) cognitive functions critical for the development of addiction, such as working memory, attention, reward evaluation, emotion, pain, and stress. It is important to note that the construct of individual difference here encompasses normal variations in function and dysfunction (or vulnerability). For the purpose of this review, we will not dissociate the contribution of the individual from the contribution of the situation in the development of individual differences because both can lead to dysregulated behavior and increased risk for the development of drug dependence.

Different types of drug users also exist. For example, different types of tobacco users have been identified, including individuals who initially limit their intake but progressively escalate

their intake and develop a strong dependence on tobacco; individuals who smoke regularly but who will always limit their tobacco intake (defined as nondependent "chippers"); and individuals who limit their intake but who will experience periods of high intake and high dependence on tobacco (Kassel et al., 1994). These different patterns of drug use and addiction suggest that the addiction process is not a unitary process and that different neuropsychobiological mechanisms may explain different drug use patterns that may ultimately lead to compulsive drug seeking and drug taking.

Animal Models

Animal models of the major components of the addiction cycle have been established and validated. The *binge/intoxication* stage can be modeled by acquisition of drug self-administration under limited access conditions (Piazza and Le Moal, 1996), brain stimulation reward (Kornetsky and Esposito, 1979), conditioned place preference (Carboni and Vacca, 2003), and drug discrimination (Holtzman, 1990). The *withdrawal/negative affect* stage can be modeled by intracranial self-stimulation (Epping-Jordan et al., 1998), conditioned place aversion (Stinus et al., 1990), drug discrimination (Holtzman, 1990), and drug self-administration in dependent subjects (Denoble and Begleiter, 1976; Gellert and Sparber, 1977). The *preoccupation/anticipation* stage can be modeled by drug self-administration and different paradigms, such as resistance to extinction (Schuster and Woods, 1968), drug-, stress-, or cue-induced reinstatement (Shaham et al., 2003), protracted abstinence (Roberts et al., 2000), conditioned withdrawal (Wikler and Pescor, 1967), and second-order schedules of reinforcement (Katz and Goldberg, 1991). Moreover, animal models of the transition to addiction that incorporate these three stages have also been developed and validated. These models include escalation in drug self-administration with extended access to the drug (Ahmed and Koob, 1998), the alcohol and nicotine deprivation effect (George et al., 2007; Koob, 2000), and drug seeking and drug taking in the presence of negative consequences (Deroche-Gamonet et al., 2004; Vanderschuren and Everitt, 2004).

Control and Cognitive Modules in Addictions

At the social psychology level, failure of self-regulation has been argued to be one of the main causes of psychosocial pathologies, including addiction (Baumeister, 2003b). Failure of self-regulation represents a deficit in information-processing, attention, planning, reasoning, self-monitoring, or inhibition of a specific brain function or behavior (Baumeister et al., 1994; Giancola et al., 1996a, b). Depending on the different stages of the addiction cycle, failure of self-regulation may lead to an increased risk of exposure to the drug, increased drug seeking and drug taking, increased relapse, or increased vulnerability to the transition to addiction. Failure of self-regulation is hypothesized to result at the neurobiological level in a loss of control of a brain structure over specific neural systems underlying relatively independent brain functions, such as stress, anxiety, reward, pain, habits, and decision-making. This loss of control has often been attributed to a dysfunction of the frontal lobes or hypofrontality (Bechara, 2005; Mishkin, 1964; Pribram, 1956) and subsequent dysregulation of the different subcortical cognitive systems controlled by the prefrontal cortex. For instance, deficits in frontal cortex regulation in children or young adolescents predict later drug and alcohol consumption, especially for children raised in families with drug and biobehavioral disorders histories (Dawes et al., 1997; Aytaclar et al., 1999).

Cognition and its neural representations have been hypothesized to be organized into a set of modules that are specialized for distinct cognitive processes and different types of information processing (Fodor, 1983). The theory of "modularity of mind" describes mind as composed of several insulated modules that are relatively independent in their functioning. These modules have separate classes of input and information processing inside each module and theoretically cannot be influenced by the activity of another module (Fodor, 1983). Imaging, brain lesion,

and neuropharmacological studies have demonstrated in both humans and animals the modularity of cognition. Classical examples of modularity are the high specificity of activation of cortical areas during the presentation of words, colors, faces, or places (Gazzaniga et al., 2000) or the dissociation between conditioning and declarative knowledge after lesions of the amygdala and hippocampus (Bechara et al., 1995). The modularity of mind theory has also been reinforced by brain lesion studies demonstrating double and even triple dissociations between different brain functions, such as explicit *vs*. implicit memory (Cohen et al., 1980), conditioning and declarative knowledge (Bechara et al., 1995), memory *vs*. fear *vs*. anxiety (Bannerman et al., 2004), pain affect and sensation (Ploner et al., 1998), and reward *vs*. motivation (Berridge et al. 2009). It is now well established that sensation, perception, motor action, or even different types of memories represent different cognitive modules with different neural systems that are more or less independent in their functioning. Flexible, goal-directed behavior requires an adapted cognitive control system for organizing, selecting, and consolidating information that derives from the different modules into a coherent and unified experience. The prefrontal cortex and its different subregions have been hypothesized to represent this cognitive control system (Baddeley, 1996; Robbins, 2000; Ridderinkhof et al., 2004).

The prefrontal cortex sends projections to most cortical and subcortical structures and targets the main sources of major diffiuse neurotransmitter systems, including the dopaminergic, noradrenergic, serotoninergic, and cholinergic neurons in the basal forebrain and brainstem (Goldman-Rakic, 1987; Gabbot et al., 2005). Moreover, neuroanatomical, brain lesion, and site-specific pharmacological modulation studies of the prefrontal cortex have revealed the heterogeneity of the prefrontal cortex (Robbins, 2000).

As explained above, there are important individual differences in the different stages of addiction and in key brain functions critical for the development of addiction, such as attention, decision-making, reward, emotion, pain, and stress (Crowley et al., 1998; de Wit et al., 1986; Deroche-Gamonet et al., 2004). We suggest that the concept of self-regulation, combined with the concept of modularity of cognitive function, may help one understand the neural basis of the individual differences in the vulnerability to drug addiction. Indeed, dysfunction of a specific subregion of the prefrontal cortex may lead to a loss of control over a specific neurobiological system, leading, for instance, to a sensitization of insentive salience in one individual and to a hyperreactivity of the stress system in another individual. Therefore, the failure of a specific module may differ from one individual to another and may represent a neuropsychobiological mechanism underlying individual differences in the vulnerability to drug addiction.

Neural Systems and Cognitive Modules

Numerous reports have demonstrated a role for the dopamine, corticotropin-releasing factor (CRF), opioid, serotonin, γ-aminobutyric acid (GABA), cholinergic, adrenergic, glutamatergic, and peptidergic systems in drug addiction (Koob and Le Moal 2006). Many reports have also demonstrated a role for the ventral tegmental area (VTA), central (CeA) and basolateral (BLA) nuclei of the amygdala, bed nucleus of the stria terminalis (BNST), dorsal and ventral striatum (nucleus accumbens), ventral pallidum, hypothalamus, and prefrontal cortex in drug addiction (Koob and Volkow 2010). The identification of drug addiction as a brain disease has oriented research in the addiction field toward a search for a common final pathway to explain the transition to addiction. Significant breakthroughs have been made, suggesting that there are common neurobiological mechanisms in all types of addictions. Converging lines of evidence suggest that a dysregulation of the dopaminergic system, CRF system, or ΔFosB may mediate the transition to addiction (for review, see Everitt and Robbins, 2005; Koob and Le Moal, 2008; Nestler, 2001; Robinson and Berridge, 1993). However, the

number of neurotransmitter systems, brain structures, and different physiological, psychological, and cognitive mechanisms involved in the addiction process suggests that understanding individual differences in the transition to addiction may require a more integrated modular view of the neuropsychological mechanisms of addiction.

The thesis of this review is that drug addiction involves a failure of the different subcomponents of the executive systems controlling key systems that process reward, pain, stress, dysphoria, and habits. A subhypothesis is that the different patterns of drug addiction and individual differences in the transition to addiction may emerge from differential vulnerability in one or more of the subcomponents. A multi-system framework with a focus on different psychological and computational vulnerabilities has been recently formulated to explain patterns of addiction across drugs and individuals (Redish et al., 2008). The focus of the present review is instead on the elaboration of a multi-system framework with a focus on the different neurobiological systems that may be differentially involved in the addiction process. In the following sections we will briefly review the neuroanatomy and function of the modules and review how individual differences in the functioning of these modules may explain individual differences in the transition to addiction. It is important to note that the modules described here are not Fodorian in the sense that they are not fully encapsulated (Fodor 1983). However, they share many properties of Fodorian modules, such as domain specificity, mandatory operation, limited accessibility, fast processing, and fixed neural architecture, and they exhibit specific breakdown patterns (see examples of double dissociation described above).

Incentive Salience and the Mesolimbic Dopamine Module

Neuroanatomy and Function—The mesolimbic dopamine system is formed by dopaminergic cell bodies in the VTA and their projections to the ventral striatum (Fig. 1). The VTA also possesses a population of GABAergic neurons that provide inhibitory inputs to dopamine cells and influence other structures, such as the pedunculopontine tegmental nucleus and glutamatergic neurons (Dobi et al., 2010). The VTA receives its main excitatory glutamatergic and cholinergic inputs from the ventromedial prefrontal cortex (ventral prelimbic, infralimbic, dorsal peduncular cortices), ventral subiculum, subthalamic nucleus, parabrachial nucleus, pedunculopontine tegmental nucleus, and laterodorsal tegmental nucleus (Kalivas, 1993). The VTA also receives prominent inputs from the nucleus accumbens shell and the ventromedial ventral pallidum (Oades and Halliday 1987). Dopamine and GABA neurons in the VTA have been shown to be critical for the rewarding properties of psychostimulants, and with the possible exception of opioids, all drugs of abuse when self-administered acutely stimulate the dopaminergic system and increase dopamine release in the nucleus accumbens (Volkow et al., 2002). The pattern of firing of dopaminergic neurons in the VTA in response to drugs of abuse has been hypothesized to encode drug reward, attribution of incentive salience, and establishment of response habits (Wise, 1980,1987,2002). Attribution of incentive salience refers to a process that transforms sensory information about reward into attractive incentives (Robinson and Berridge, 1993). Individual differences in incentive salience may represent a key mechanism to explain individual differences in the vulnerability to addiction, and excessive attribution of incentive salience to drug-related cues may contribute to excessive drug intake, compulsive behavior, and relapse.

Individual Differences—There are considerable individual differences in the reinforcing properties of drugs of abuse in humans and animals (de Wit et al., 1986; O'Brien CP, 1986). The acute rewarding effects of drugs of abuse are critical in nondependent users and represent a powerful source of positive reinforcement for the initiation and maintenance of drug self-administration. Individual differences in the mesolimbic dopamine system have been observed in humans and have been related to differential anticipation and reward-seeking behavior. Individual differences in dopamine D_2 receptor binding in the ventral/dorsal striatum suggest

differential activity of the mesolimbic dopamine system (Volkow et al., 1993). Individual differences in amphetamine-induced dopamine release are associated with increased drug-induced "wanting" and novelty-seeking (Leyton et al., 2002). Higher ratings of positive amphetamine effects are also associated with greater dopamine release in the ventral striatum, dorsal putamen, and dorsal caudate (Oswald et al., 2005). Baseline D_2 receptor availability in the striatum negatively predicts rates of cocaine self-administration in monkeys (Nader et al., 2006).

Individual differences in the sensitivity of the VTA to electrical self-stimulation has been observed and related to differential sensitivity of the reward system (Druhan et al., 1990). Moreover, rats that show increased novelty-seeking and increased cocaine self-administration also show dysregulation of tyrosine hydroxylase and cholecystokinin in the VTA (Lucas et al., 1998), increased basal firing rates of dopamine neurons in the VTA (Marinelli and White, 2000), and increased basal or drug-induced dopamine release in the nucleus accumbens (Bradberry et al., 1991; Hooks et al., 1992; Piazza et al., 1991b; Rouge-Pont et al., 1998). Furthermore, individual differences in dopamine transporters in the VTA and dopamine and serotonin levels in the striatum have been associated with individual differences in behavioral sensitization to amphetamine (Antoniou et al., 2008; Dietz et al., 2008; Piazza et al., 1991b). These results suggest that the mesolimbic dopamine system and the ventral striatum may represent a key system for the vulnerability to the positive reinforcing effects of drugs and the initiation and maintenance of drug self-administration.

Stress and the Hypothalamic-Pituitary-Adrenal Axis

Neuroanatomy and Function—The hypothalamic-pituitary-adrenal (HPA) axis is defined by three major structures: the paraventricular nucleus of the hypothalamus (PVN), the anterior lobe of the pituitary gland, and the adrenal gland (for review, see Turnbull and Rivier, 1997). Neurosecretory neurons in the medial parvocellular subdivision of the PVN synthesize and release CRF into the portal blood vessels that enter the anterior pituitary gland. Binding of CRF to the CRF_1 receptor on pituitary corticotropic cells induces the release of adrenocorticotropic hormone (ACTH) into the systemic circulation (Fig. 1). ACTH, in turn, stimulates glucocorticoid synthesis and secretion from the adrenal cortex. Vasopressin released from parvocellular neurons of the PVN produces synergistic effects on ACTH release that are mediated by vasopressin V_{1b} receptors (Scott and Dinan, 1998). The HPA axis is finely tuned via negative feedback from circulating glucocorticoids that act on the glucocorticoid receptor, a cytosolic protein that acts via the nucleus on transcriptional mechanisms in two main brain areas: the PVN and the hippocampus (Herman et al., 1996). The hypophysiotropic neurons of the PVN are innervated by numerous afferent projections from the brainstem, other hypothalamic nuclei, and forebrain limbic structures. The medial prefrontal cortex in the rat possesses a large number of glucocorticoid receptor-positive neurons that can bidirectionally control stress reactivity of the HPA axis through activation of the prelimbic or infralimbic cortex (Radley et al., 2006). Lesions of the prelimbic cortex increase ACTH and corticosterone responses to stress, whereas lesions of the infralimbic cortex have an opposite effect (Radley et al., 2006). This differential control is attributable to differential projections of the prelimbic and infralimbic cortex to structures mediating either stress inhibition (ventrolateral preoptic area, dorsomedial hypothalamus, and PVN) and stress activation (anterior BNST, medial nucleus of the amygdala; CeA, and nucleus of the tractus solitarus), respectively (Radley et al., 2006).

The HPA axis plays a key role in mediating the reinforcing effects of drugs of abuse and stress-induced relapse. Drugs of abuse acutely activate the HPA axis, and dependence dysregulates the HPA axis (Piazza and le Moal 1996). Stressors facilitate the acquisition of cocaine and amphetamine self-administration, and rats with heightened reactivity to stress acquire drug

self-administration faster and at lower doses (Piazza et al., 1989; Piazza and Le Moal, 1998; Piazza et al., 1991a; Piazza et al., 1996). Moreover, corticosterone facilitates the acquisition of cocaine self-administration (Mantsch et al., 1998; Piazza et al., 1991a). The effect of glucocorticoids on the reinforcing effects of drugs is hypothesized to be attributable to activation of dopamine neurons in the VTA and increased dopamine release in the nucleus accumbens (Barrot et al., 2001; Barrot et al., 2000; Piazza and Le Moal, 1998). Furthermore, excessive drug intake and possibly the transition to dependence are associated with tolerance of the HPA axis response to stress and overactivation and persistent dysregulation during early withdrawal and protracted abstinence (Mantsch et al., 2003; Zhou et al., 2003a; Zhou et al., 2003b). Interestingly, the HPA axis also interacts with the extended amygdala. High circulating levels of glucocorticoids can activate the CRF and norepinephrine systems in the CeA and BLA through a positive feedback mechanism (Imaki et al., 1991; Makino et al., 1994; Swanson and Simmons, 1989). These results suggest that the HPA axis may be involved in both the initial positive reinforcing effects of the drug and on the vulnerability to relapse after protracted abstinence, particularly during stressful events (Erb et al., 1996, 1998; Martin-Fardon et al., 2000).

Individual Differences—Individual differences in the responsivity of the HPA axis to stress are very well understood. Sensation-seeking and novelty-seeking are personality traits that have been associated with higher propensity to self-administer drugs and dysregulation of the HPA axis in humans and rodents (Piazza and Le Moal, 1998). Animal models for these traits include the characterization of high *vs*. low responders by measuring locomotor activity in an inescapable novel environment (Piazza et al., 1989). High responders are more sensitive to cocaine, amphetamine-induced locomotor activity, and amphetamine self-administration. This increased sensitivity to drugs of abuse in high responder rats has been shown to be dependent on the HPA axis. High responder rats exhibit an exaggerated corticosterone response to stress, and this increased corticosterone drives in part the increased activation of the VTA and dopamine release in the nucleus accumbens (Piazza and Le Moal, 1998; Piazza et al., 1991a). Individual differences in the HPA axis are then likely to confer vulnerability to the initial positive reinforcing effects of drugs, at least during initial drug exposure and the acquisition of self-administration, but not necessarily vulnerability to dependence *per se*. Indeed, recent reports suggest that although heightened reactivity of the HPA axis is associated with a vertical shift in the cocaine dose-response curve and increased self-administration during acquisition, it is not associated with increased compulsive cocaine intake (Belin et al., 2008; Deroche-Gamonet et al., 2004). Moreover, the effect of stress on relapse does not appear to be directly mediated by the HPA axis but rather indirectly by the extrahypothalamic CRF system through a CRF-CRF_1 receptor connection between the CeA and ventral BNST (Erb et al., 1998; Erb and Stewart, 1999; Le et al., 2002; Le et al., 2000; Shaham et al., 1997; Shalev et al., 2009) and the noradrenergic system through a nucleus accumbens-β-adrenergic receptor connection between the lateral tegmental nucleus and BNST (Erb et al., 2000; Shaham et al., 2000). Dysregulation of the HPA axis may represent a key factor in the vulnerability to addiction by modulating two key modules. Heightened reactivity of the HPA axis may facilitate both the positive reinforcing effects of drugs via modulation of the mesolimbic dopamine system and the negative reinforcing effects of drugs by activating the extended amygdala and thus may be involved in the initiation, maintenance, and relapse of drug self-administration.

Negative Emotional States and the Extended Amygdala Module

Neuroanatomy and Function—The extended amygdala is a neuroanatomical macrostructure in the basal forebrain that shares similarities in morphology, neurochemistry, and connectivity (Fig. 1). It is composed of the BNST, CeA, MeA, and a transition zone in the posterior medial part (shell) of the nucleus accumbens (Koob and Le Moal, 2001). This system receives afferents from limbic and olfactory cortices. Key inputs are the insular cortex and the

ventral medial prefrontal cortex (ventral prelimbic, infralimbic, and dorsal peduncular cortices), lateral hypothalamus, parabrachial nucleus, lateral tegmental nucleus, and BLA either through direct or indirect projections via the GABAergic intercalated cell mass (Gray et al., 1993;Reynolds and Zham, 2005; Alheid and Heimer, 1998; Koob et al., 1998) (Fig. 1). The extended amygdala projects heavily to the lateral hypothalamus, ventral pallidum (posterior medial), VTA, pedunculopontine tegmental nucleus, parabrachial nucleus, lateral tegmental nucleus, and other midbrain structures (Gray et al., 1993;Reynolds and Zham, 2005; Alheid and Heimer, 1998; Koob et al., 1998). As such, the extended amygdala links the basal forebrain to the classic reward systems of the lateral hypothalamus via the medial forebrain bundle reward system. Key elements of the extended amygdala include neurotransmitters of the brain stress systems associated with the negative reinforcement of dependence, such as CRF and norepinephrine (Koob and Le Moal, 2005). Studies on fear and anxiety have identified the amygdala as a central component of the processing of fear, threats, and anxiety in humans and animals (Koob and Le Moal, 2008;LeDoux, 2000). The extended amygdala is hypothesized to engage the organism in fight or flight responses and to encode negative emotional states. Dysregulation of the extended amygdala has been hypothesized to play a key role in disorders related to stress and negative emotional states, such as posttraumatic stress disorder, general anxiety disorder, phobias, and affective disorders (Shin and Liberzon, 2010). Neuroadaptive changes in this extended amygdala circuit may also lead to the aversive effects and dysregulated reward system hypothesized to be the motivation for the transition to drug addiction (Koob and Le Moal, 2008).

Individual Differences—Converging evidence suggests that there are major individual differences in the response of the extended amygdala to emotional stimuli (Beaver et al., 2008; Bishop et al., 2004; Canli, 2004; Canli and Gabrieli, 2004; Hamann and Canli, 2004; Mather et al., 2004). Individual differences in a personality trait linked to the drive to gain reward (increased reward-drive) correlate positively with activation of the amygdala and negatively correlated with activity in the ventromedial prefrontal cortex (Beaver et al., 2008). A heightened predisposition to aggression is also associated with an increased amygdala response to aggressive facial displays (Coccaro et al., 2007; Passamonti et al., 2008). The CeA (dorsal amygdala in humans) is also recruited during conscious processing of fearful faces in healthy volunteers, and individual differences in trait anxiety predict the response of a key input to the CeA, the BLA, to unconsciously processed fearful faces (Etkin et al., 2004). The amygdala is also activated during affective judgment and during the expression of emotional responses when viewing affective pictures (Phan et al., 2003; Taylor et al., 2003). Moreover, the amygdala is activated during drug craving (Childress et al., 1999; Kilts et al., 2001; Volkow et al., 1999; Wang et al., 1999; Wexler et al., 2001), and decreased amygdala volumes (Makris et al., 2004) and abnormalities in the fiber tracts connecting the orbitofrontal cortex and anterior cingulate cortex to the amygdala have been observed in some cocaine addicts (Lim et al., 2002). Interestingly, the changes in amygdala volume in cocaine addicts were observed even in subjects recently exposed to cocaine (<1–2 years), suggesting that decreased amygdala volume represents either early drug-induced impairment or an individual developmental predisposition (Lim et al., 2002).

Individual differences have also been observed in rodents. Differences in anxiety-like behavior have been related to differential levels of vasopressin and androgen receptors (Linfoot et al., 2009), glucocorticoid receptors, and cholecystokinin-B receptors (Wunderlich et al., 2002) in the extended amygdala. Individuals with increased anxiety-like responding exhibited a downregulation of amygdala cholecystokinin-B receptor binding, possibly reflecting compensation for increased cholecystokinin activity (Wunderlich et al., 2002). Individual differences in the sensitivity of the CeA to inactivation by a $GABA_A$ receptor agonist have also been observed in rats self-administrating amphetamine. Inactivation of the CeA only decreased amphetamine self- administration in rats with excessive drug intake, suggesting that

individual differences in the recruitment of the CeA might predispose an individual to excessive drug intake (Cain et al., 2008). Altogether, these results demonstrate that individual differences in the activity of the extended amygdala may predispose individuals to heightened anxiety, stress, and a negative emotional state and represent a key factor in the transition from positive to negative reinforcement and the transition to addiction.

Pain and the Opioid Spinomesothalamocortical Module

Neuroanatomy and Function—Pain is a subjective experience that has a powerful influence on decision-making and can dramatically alter the reinforcing effects of drugs of abuse, particularly opiates, and facilitate the transition to drug addiction (Miller and Gold 2007). Pain is a multidimensional phenomenon that includes acute pain, chronic pain, and emotional pain as well as different types of pain based on different noxious stimuli (e.g., chemical, heat, mechanical). The neural substrates of acute and chronic pain have been extensively studied using imaging techniques in humans and rodents (Peyron et al., 2000; Porro, 2003; Vogt, 2005). Key areas involved in the processing of acute and chronic pain involve the spinoreticular, spinomesencephalic, and spinothalamic tract, parabrachial nuclei, periaqueductal gray area (PAG), rostroventromedial medulla, medial and ventroposterolateral thalamus, centrolateral, centromedian, and parafascicular nucleus of the thalamus, amygdala, somatosensory cortex, insular cortex, and anterior cingulate cortex (Fig. 1) (Peyron et al., 2000; Porro, 2003; Vogt, 2005). Pain is associated with activation of a primary afferent nociceptor that transmits pain signals to a second-order neuron in the dorsal horn that crosses contralaterally and sends efferents to the brainstem, thalamus, and neocortex. Some have argued that the classic pain pathway (spinothalamocortical) mediates physical pain, whereas the affective component of pain is mediated by the extra-spinothalamocortical pathway (Besson, 1999; Price, 2000). Key regions in the processing of emotional pain in this pathway are the parabrachial nucleus, CeA, PAG, insula, and anterior cingulate cortex (Besson, 1999; Price, 2000). Chronic and acute pain is associated with hyperactivity of the dorsal horn and spinothalamic tract, resulting in activation of the neocortex as well as hyperactivity of the parabrachial nucleus and CeA (Han and Neugebauer, 2004). Moreover, the CeA can control pain through a descending projection to the PAG and rostroventromedial medulla that can modulate nociceptive relay neurons in the dorsal horn (Gaurieau and Bernard, 2002). The main neurotransmitter mediating control over pain signals through the descending pathways is the endogenous opioid enkephalin. Enkephalin acts through activation of the μ-opioid receptor, and μ-opioid-induced analgesia is hypothesized to be mediated at different levels of the descending pathways (hypothalamus, amygdala, and PAG) (Fields, 2000). Interactions between pain and the motivation to obtain drugs have been demonstrated, particularly for opiate and alcohol addiction. For example, in rats with hypersensitivity of the hindpaw to mechanical stimulation, only heroin doses that produce a reversal of hypersensitivity maintained heroin self-administration following nerve injury, whereas lower doses were only effective in maintaining drug self-administration in control rats (Martin et al., 2007), suggesting that the driving force for the motivation to self-administer drugs in individuals with a sensitized pain system may be seeking relief of chronic pain.

Individual Differences—Individual differences have been well described in pain studies. Pain thresholds greatly vary with gender, age, and the subject's behavioral state (Fillingim et al., 2009; Gibson and Helme, 2001; Nielsen et al., 2009). For instance, under great emotion or intense concentration, people often report few signs of pain despite severe injuries (Fields, 2004). Imaging studies have shown that activity in the midbrain, medial thalamus, and cortical nociceptive-receiving areas such as the insula and anterior cingulate cortex correlate with pain intensity (Casey, 2000). Individuals with low pain thresholds exhibit higher activation of the primary somatosensory cortex, anterior cingulate cortex, and prefrontal cortex than individuals with high pain thresholds (Coghill et al., 2003). Interestingly, individual differences did not

correlate with differential activation of the thalamus despite its key involvement in the encoding of nociceptive information (Coghill et al., 2003). Moreover, the impact of perceived controllability on pain perception varies highly between individuals and is correlated with differential activation of the anterior cingulate cortex, insula, and ventrolateral prefrontal cortex (Salomons et al., 2007). Activity in the anterior cingulate cortex, dorsolateral prefrontal cortex, insular cortex, nucleus accumbens, thalamus, and PAG correlated with the magnitude of placebo analgesia in humans (Wager et al., 2004; Zubieta et al., 2005) and is mediated in part via activation of the endogenous opioid system, specifically activation of μ-opioid receptors (Zubieta et al., 2005). Abnormal pain perceptions have been reported in opiate addiction during the development, maintenance, and withdrawal periods (Compton, 1994; Compton et al., 2000; Compton and Estepa, 2000; Doverty et al., 2001a; Doverty et al., 2001b), and preexisting pain problems are a key factor in the transition to opiate abuse and addiction (Brands et al., 2004). Altogether, these results suggest that dysregulation of the pain system, particularly the insula, anterior cingulate cortex, and CeA, because of the cross between “affective” pain pathways there and negative emotional states, might confer vulnerability to drug addiction in some individuals.

Habits and the Striatal Module

Neuroanatomy—The striatum in rodents can be divided into several components, including the ventral striatum (nucleus accumbens shell and core) and dorsal striatum (dorsomedian and dorsolateral) (Fig. 1). The striatum is composed of inhibitory GABAergic cells projecting to the pallidum (95% of striatal cells) and the brainstem and local cholinergic interneurons (5% of striatal cells) (Gerfen, 1992). The connectivity of the striatum is organized on a ventromedial to dorsolateral axis (Voorn et al., 2004). The nucleus accumbens shell receives dopaminergic inputs from the VTA and glutamatergic inputs from the ventromedial ventral PFC (ventral prelimbic, infralimbic, dorsal peduncular cortices) and insular cortex and projects to the ventromedial part of the ventral pallidum and VTA (Reynolds and Zahm 2005;Gabbot et al., 2005). The nucleus accumbens core receives dopaminergic inputs from the VTA and glutamatergic inputs from the dorsomedial prefrontal cortex (dorsal prelimbic, anterior cingulate cortex) and insular and orbital frontal cortices and projects to the dorsolateral part of the ventral pallidum and dorsomedial substantia nigra (Reynolds and Zahm 2005;Gabbot et al., 2005). The dorsomedial and dorsolateral striatum receives glutamatergic inputs from the orbitofrontal cortex, anterior cingulate cortex, and sensory and motor cortices and projects to the globus pallidus and ventrolateral substantia nigra (Reynolds and Zahm 2005;Gabbot et al., 2005). The striatum and cortico-striato-pallido-thalamic loops have generally been studied for their role in locomotor activity, attention, reward, goal-directed behavior, and habits. These loops have inputs from the mesolimbic and mesostriatal systems and are partially overlapping and organized in a ventral-to-dorsal manner (Voorn et al., 2004). Recent reports suggest that these striatal loops are involved in the maintenance of drug-seeking behavior under a second-order schedule of reinforcement and might be important for addiction (Belin and Everitt, 2008). A ventral system, including the ventral striatum and its inputs from the orbitofrontal cortex, infralimbic cortex, hippocampus, amygdala, and VTA, is key for the acquisition of instrumental responding, such as the acquisition of cocaine self-administration (Belin et al., 2009). A dorsomedial system, including the dorsomedial striatum and inputs from the anterior cingulate cortex and prelimbic cortex, and premotor cortices may be key for goal-directed behavior in general. A dorsolateral system, including the dorsolateral striatum and its somatosensory inputs and connections with the mesostriatal dopaminergic system, may underlie habit responding (Belin et al., 2009). Recent studies suggest that the transition to drug dependence is associated with a progressive dysregulation of the ventral, dorsomedial, and dorsolateral striatal systems mediating the transition from impulsive to compulsive drug-seeking and drug-taking (Belin and Everitt, 2008).

Individual Differences—Individual differences have been largely reported at the behavioral level in the acquisition of instrumental behavior, goal-directed behavior, and habit responding (Boakes, 1977; Tomie et al., 2000; Zener, 1937) and have been related to individual differences in dopamine levels and D_1 receptor mRNA in the dorsal and ventral striatum (Cheng and Feenstra, 2006; Flagel et al., 2008; Tomie et al., 2000). Individual differences have been observed not only in terms of quantitative but also qualitative differences. Indeed, subjects can adopt different strategies for solving problems (goal-directed *vs*. habit) to reach similar performance levels in behavioral tasks even when both strategies are successful. When constrained to only one strategy, important performance differences can be observed, suggesting individual differences in the functioning of the striatum and corticostriatopallidothalamic loops (Flagel et al., 2007).

Impulsivity, escalation, and compulsivity are hypothesized to represent the different steps of a continuum of behavioral alterations that are observed during the transition to addiction, reflected in the development of the inflexible and habit-like behavior associated with drug seeking in nondependent subjects and drug taking in dependent subjects, respectively (Dalley et al., 2007). Low D_2 receptor binding in the ventral striatum predicts the magnitude of cocaine intake escalation and compulsive cocaine intake when rats are given extended but not limited access to cocaine (Dalley et al., 2007a). Moreover, detoxified drug abusers exhibit decreased D_2 receptor binding in the ventral striatum that correlates with self-reported preference for methylphenidate (Volkow et al., 1999). In compulsive cocaine users, individual differences in craving after methylphenidate injection in cocaine abusers have also been demonstrated and correlate with increased metabolic activity in the striatum and orbitofrontal cortex (Volkow et al., 1999). Individual differences in D_2 binding in the striatum have also been reported between subordinate and dominant monkeys, and there appears to be an inverse relationship between D_2 receptor levels and vulnerability to the reinforcing effects of cocaine (Nader et al., 2005). Subordinate monkeys exhibit lower D_2 receptor binding (Grant et al., 1998; Morgan et al., 2002) and increased cocaine intake (Morgan et al., 2002). Altogether, these results suggest that individual differences in the ventral and dorsal striatum may underlie both the vulnerability to the positive reinforcing effects of the drug and the vulnerability to the transition from goal-directed to compulsive drug seeking.

Decision-Making and the Prefrontal Cortex Module

Neuroanatomy—The prefrontal cortex in rodents can be dissociated into medial, lateral, and ventral parts (Fig. 2) (Robbins, 2000). The medial PFC is composed of a dorsal section with the anterior cingulate, precentral, and dorsal prelimbic cortices and a ventral section with the ventral prelimbic, infralimbic, dorsal peduncular, and medial orbital cortices. The lateral PFC is composed of the orbitofrontal cortex and the dorsal and ventral anterior insular cortices. The ventral PFC is composed of the ventral orbital and ventral lateral orbital cortices. The main output of the prefrontal cortex is composed of excitatory glutamatergic pyramidal neurons (Goldman-Rakic, 1987). Pyramidal neurons are under tight control by local GABAergic inhibitory interneurons (Wilson et al., 1994;Rao et al., 2000). The different subregions of the prefrontal cortex send and receive highly organized connections with the basal ganglia through the cortico-striato-pallido-thalamo-cortical and cortico-pallido-nigro-thalamo-cortical loops (Groenewegen et al., 1997;Voorn et al., 2004). Through its different subregions, the PFC can control virtually all of the subcortical structures through the modulation of the cholinergic, dopaminergic, adrenergic, and serotonergic systems by activating basal forebrain and brainstem nuclei through a direct glutamatergic projection or by inhibiting the same structures via activation of local inhibitory GABAergic interneurons.

The prefrontal cortex has a key role in cognitive functions involved in decision-making, including, but not limited to, memory, attention, emotion, working memory, outcome

expectation, and planning. Impairment of decision-making is a key feature of addiction. Compulsive drug taking can also be viewed as an aberrant behavior resulting from poorly modulated decisions due to the inability to learn from the negative consequences of drug use. The prelimbic and infralimbic cortices in rats maintain stimulus representation during delays (working memory) and are critical for inhibition of behavior during extinction of a Pavlovian conditioned response to allow motivationally based decision-making (Morgan and LeDoux, 1999; Narayanan et al., 2006; Sakurai and Sugimoto, 1985). The prelimbic cortex is also important for detecting action-outcome contingencies and thus goal-directed actions (Balleine and Dickinson, 1998), whereas the infralimbic cortex may be important for learning stimulus-response associations or habit behavior (Killcross and Coutureau, 2003). Studies in humans have also demonstrated that the medial prefrontal cortex (including Brodman's Areas 10, 32, and 25) is a critical structure in the neural system subserving risky decision-making (Damasio et al., 1994; Glimcher and Rustichini, 2004). Moreover, two systems can be identified: the ventral medial prefrontal cortex (which encodes decisions based on reward value) and the dorsal medial prefrontal cortex (which encodes decisions based on risk). The orbitofrontal cortex is critical in guiding behavior by signaling outcome expectancy when representation of the value of the expected outcome needs to be compared to an alternative response or needs to be held in memory (Schoenbaum et al., 2006).

Individual Differences—Individual differences in functioning of the prefrontal cortex and decision-making have been observed using behavioral testing, imaging, and neurochemistry techniques in humans and animals. Converging evidence shows that individual differences in prefrontal cortex activity and dopamine, acetylcholine, norepinephrine, and serotonin tone in the prefrontal cortex correlate with working memory, visual attention, and impulsivity in rats (for review, see Dalley et al., 2004). Imaging studies in humans have shown that individual differences in decision-making under risk correlate with activity in the ventromedial prefrontal cortex (Tom et al., 2007), and individual risk preference in a risky decision-making task negatively correlates with activity in the dorsal medial prefrontal cortex and positively correlates with activity in the ventral medial prefrontal cortex (Xue et al., 2009). Individuals with strong activation of the dorsal medial prefrontal cortex are more sensitive to risk and therefore less likely to make risky decisions, whereas individuals with strong activation of the ventromedial prefrontal cortex are more sensitive to reward and more likely to make risky choices (Xue et al., 2009). Individual differences in preferred strategies in a decision-making task (i.e., maximizing gain or minimizing losses) can be predicted by activation of the ventromedial prefrontal cortex and anterior insula, respectively (Venkatraman et al., 2009). Moreover, suppression of cortical excitability in the right dorsolateral prefrontal cortex using transcranial magnetic stimulation induces risky behavior (Knoch et al., 2006), and the interhemispheric balance of activity across the dorsolateral prefrontal cortex may mediate poor decision-making in individuals involved in risky behavior (Fecteau et al., 2007a; Fecteau et al., 2007b). These results suggest that individual vulnerability in the prefrontal cortex may lead to impaired decision-making and facilitate the initiation and maintenance of drug self-administration.

Loss of Control and the Prefrontal Cortex Module

Loss of control over drug use is a hallmark feature of drug addiction. Loss of control has been attributed to a dysfunction of the prefrontal cortex, based on neuroimaging studies in humans (London et al., 2000; Koob and Volkow 2010). Studies in rats show that loss of control over drug use is progressively established after extended access to self-administration (Ahmed and Koob, 1998; Deroche-Gamonet et al., 2004) and can be predicted by high impulsivity (Belin et al., 2008; Dalley et al., 2007a). Despite accumulating evidence that limited drug exposure induces neuronal changes in the prefrontal cortex (Ben-Shahar et al., 2007; Bowers et al., 2004; Crespo et al., 2002), there was little evidence, until recently, of long-lasting neuronal

adaptations of the prefrontal cortex in animal models of the loss of control over drug use (Ben-Shahar et al., 2007; Ferrario et al., 2005; Seiwell et al., 2007). Moreover, recent reports demonstrated that at least in one model of loss of control (i.e., extended access to cocaine self-administration) there were no long-lasting impairments of prefrontal cortex cognitive function, such as response inhibition and sustained attention (Dalley et al., 2005; Dalley et al., 2007b). An alternative hypothesis is that extended access to cocaine produces deficits in other cognitive functions relevant to decision-making mediated by the prefrontal cortex that are operating under high cognitive demand and high-incentive conditions. A condition with high cognitive demand in this context refers to an experimental paradigm in which the cognitive processes necessary to solve a task reach their limit or capacity, whereas a high-incentive condition refers to an experimental paradigm that motivates a high degree of approach behavior due to the high attractiveness of the positive reinforcer. These conditions may particularly challenge the dorsomedial prefrontal cortex and orbitofrontal cortex. Moreover, working memory under a high-incentive condition has been shown to be a sensitive measure of the integrity of the prefrontal cortex (Krawczyk et al., 2007; Taylor et al., 2004).

Recent studies using animal models of compulsive drug use demonstrated that independent of any premorbid condition, a history of drug dependence induced persistent impairments in working memory (George et al., 2008) and sustained attention (Briand et al., 2008) that correlated with decreased density of neurons and oligodendrocytes but not astrocytes in the dorsomedial and orbital prefrontal cortex (George et al., 2008), dopamine D_2 receptor mRNA in the medial and orbital prefrontal cortex, and D_2 receptor protein in the medial prefrontal cortex (Briand et al., 2008). Additionally, long-lasting alterations in *N*-methyl-D-aspartate (NMDA) function have also been observed in these models (Ben-Shahar et al., 2009). Interestingly, working memory impairments were only observed under high cognitive demands and high incentive conditions, suggesting an imbalance between a hypoactive cognitive system that controls decision-making under high cognitive demands and an overactive incentive salience system (Bechara, 2005). An intriguing finding was that working memory impairments were not predicted by the amount of cocaine intake but rather by the relative increase in excessive cocaine intake compared with baseline self-administration under limited access conditions (George et al., 2008). These results suggested that prefrontal cortex dysfunction may not only be a simple consequence of drug use but may also contribute to a feed-forward mechanism in the loss of control over drug intake during the transition to drug dependence.

Loss of control and failure of self-regulation have been hypothesized to be significant contributory causes of many psychosocial pathologies, including depression, anxiety, chronic pain, posttraumatic stress disorder, eating disorders, gambling, obsessive compulsive disorders, and addiction (Baumeister, 2003). Considering the relative independence of these disorders and the differential involvement of the stress, pain, emotion, habits, decision-making, and reward systems in these disorders, it is likely that loss of control is not a unitary mechanism mediated by the prefrontal cortex. The heterogeneity of the prefrontal cortex and the segregated anatomical connections between the prefrontal cortex and the subcortical modules described above suggest that there may be multiple mechanisms of loss of control mediated by a failure of different subregions of the prefrontal cortex in controlling subcortical structures. Loss of control over stress, anxiety, reward, pain, habits, and decision-making during the different stages of addiction may lead to an increased risk of exposure to the drug, increased drug seeking and drug taking, increased relapse, and increased vulnerability to the transition to addiction.

Loss of Control Over Stress—Stress reactivity is highly dependent on whether the stress can be controlled. Stressful and aversive events are much less detrimental when the individual has control over the stress. Lack of control over stress may be a key factor in the development of anxiety, depression, posttraumatic stress disorder, and drug addiction (Amat et al., 2005). Many studies in animals have demonstrated the key role of brainstem nuclei, such as the dorsal

raphe and locus coeruleus, in encoding the response to uncontrollable stress, but control over these stress circuits may be achieved by the prefrontal cortex through a glutamatergic projection from the infralimbic and prelimbic cortex onto local GABAergic neurons in the dorsal raphe leading to powerful inhibition of serotonin neurons (Amat et al., 2005). Pharmacological inhibition of the prelimbic and infralimbic cortices in rats blocks the inhibition of dorsal raphe neurons observed under controllable stress as well as the behavioral consequence of a controllable stress, demonstrating the role of the prefrontal cortex in the control of stress (Amat et al., 2005). Individual differences in the strength of the connection between the prefrontal cortex and brainstem nuclei involved in the autonomic, psychological, and behavioral responses to stress might represent a key mechanism whereby loss of control over stress may lead to increased vulnerability to anxiety, depression, posttraumatic stress disorder, and addiction. The medial prefrontal cortex in rats has a large number of glucocorticoid receptor-positive neurons that can bidirectionally control stress reactivity of the HPA axis through activation of the anterior cingulate, prelimbic, or infralimbic cortices (Diorio et al., 1993; Figueiredo et al., 2003a; Figueiredo et al., 2003b; Sullivan and Gratton, 1999). Lesions of the prelimbic cortex increase ACTH and corticosterone responses to stress, whereas lesions of the infralimbic cortex have the opposite effect. This differential control is attributed to differential projections of the prelimbic and infralimbic cortices to structures mediating either stress inhibition (ventrolateral preoptic area, dorsomedial hypothalamus, and peri PVN; Hurley, 1991; Sesack,et al., 1989) and stress activation (anterior BNST, MeA, CeA, and the nucleus of the tractus solitarus; Hurley et al., 1991; Takagishi and Chiba, 1991), respectively. Moreover, lesions of the prelimbic cortex enhance stress-induced c-*fos* expression and CRF mRNA expression in neurosecretory neurons (related to the HPA axis) of the PVN, whereas lesions of the infralimbic cortex had opposite effects but also increased Fos induction in autonomic neurons (sympathoadrenal) of the PVN (Radley et al., 2006). Altogether, these results suggest that the dorsal prefrontal (prelimbic) cortex exerts inhibitory control over the HPA axis, whereas the ventral prefrontal cortex exerts positive control over the HPA axis while exerting inhibitory control over central autonomic responses. With regard to the control of the prefrontal cortex over the dorsal raphe, the control of the prelimbic cortex over the PVN is mediated by a GABAergic relay in the anterior BNST (Radley et al., 2009). Moreover, loss of control over the HPA axis may contribute, through a feed-forward mechanism, to hyperactivation of CRF and norepinephrine systems in the extended amygdala to produce a negative emotional state that characterizes the *withdrawal/negative affect* stage of addiction.

Loss of Control Over Emotion—Emotion plays a key role in adaptation as well as influences cognitive function and behavioral responses in a variety of situations. Emotion is often viewed as a bottom-up modulator of decision-making, learning, and memory or even pain and perception, but often neglected is the fact that processing of emotional information can also be regulated via top-down mechanisms such as suppression or reappraisal (Johnstone et al., 2007; Ochsner et al., 2002, 2004; Phan et al., 2005). Such cognitive control may downregulate neural, physiological, and behavioral responses to emotion-eliciting stimuli (Jackson et al., 2000). It is well established that recruitment of a prefrontal network, including the dorsal and ventral prefrontal cortex and orbitofrontal cortex, is necessary to reduce activation of the amygdala by emotion-eliciting stimuli (Urry et al., 2006; Johnstone et al., 2007). Glutamatergic neurons in the ventral prefrontal cortex project to GABAergic inhibitory neurons in the capsular division of the CeA and inhibit the output of the CeA (Royer and Pare, 2002). Numerous studies have demonstrated that negative emotional states can lead to impulsive aggressive behavior, that important individual differences exist in the capacity of the individual to suppress aggressive thoughts, and that this effect is under the control of the prefrontal cortex, particularly the orbitofrontal cortex, ventromedial prefrontal cortex, and dorsolateral prefrontal cortex in humans (Davidson et al., 2000). One mechanism to explain the control of the prefrontal cortex over aggressive behavior is a powerful inhibition of the

amygdala by the prefrontal cortex. Individuals who use more emotion regulation strategies, such as spontaneous reappraisal, have a lower negative emotional state and greater physical and psychological well being (Drabant et al., 2009). Individual differences in emotion regulation strategies and failure of control over emotion through hypofunction of the prefrontal cortex may represent a key neuropsychological mechanism responsible for increased vulnerability to anxiety, depression, and addiction.

Loss of Control Over Incentive Salience—Incentive salience represents a powerful mechanism that transforms neutral cues into powerful motivational magnets eliciting approach and guiding drug-related behavior (Robinson and Berridge, 1993). Intense incentive motivation attribution is considered to have a major role in different psychopathologies. Executive control over incentive salience is essential to maintain goal-directed behavior and flexibility of stimulus-response associations. The prefrontal cortex sends glutamatergic projections directly to mesocortical dopamine neurons in the VTA, exerting excitatory control on dopamine in the prefrontal cortex. Interestingly, the prefrontal cortex does not project directly onto mesolimbic dopamine neurons (Sesack and Carr, 2002). In contrast, prefrontal cortex neurons inhibit mesolimbic dopamine neurons through activation of GABAergic relay neurons in the VTA or nucleus accumbens (Carr and Sesack, 2000; Sesack and Pickel, 1992). Thus, the prefrontal cortex is in a good position to inhibit incentive salience and suppress conditioned behavior when a salient cue is presented to the subject. Consistent with this notion, it has been shown that appetitive stimuli activate the prefrontal cortex and that lesions of the prefrontal cortex induce impulsivity (Bechara et al., 2000; Jentsch and Taylor, 1999). Withdrawal from cocaine is associated with decreased prefrontal activity (Goldstein and Volkow, 2002) and extrasynaptic glutamate release as well as decreased dopamine release in the nucleus accumbens (Moussawi et al., 2009; Weiss et al., 1992). In contrast, cue-induced reinstatement of drug seeking-behavior induces a dramatic increase in prefrontal activity and glutamate release in the nucleus accumbens (Moussawi et al., 2009). The lower basal tone of the prefrontal-glutamatergic system associated with an exaggerated phasic response during relapse combined with reduced basal dopaminergic tone elicits a dramatic glutamatergic response that may mediate compulsive drug seeking by disinhibiting the control of behavior by reward-associated cues. Individual differences in prefrontal cortical control of incentive salience may represent a key mechanism to explain individual differences in the vulnerability to addiction, and excessive attribution of incentive salience to drug-related cues may lead to excessive drug intake, compulsive behavior, and relapse.

Loss of Control Over Pain—Self-regulation is a key mechanism involved in the control of both acute and chronic pain (Morley et al., 2005; Perez-Pareja et al., 2005; Solberg Nes et al., 2009). Control over pain is a key evolutionary advantage because it allows individuals to disengage from pain to fight or escape in the presence of injury. Converging evidence suggests that the prefrontal cortex mediates the control of pain. Electrical stimulation of the prefrontal cortex in rats induces antinociceptive effects (Cooper, 1975; Zhang et al., 1998), and pain stimuli and the expectancy of pain activate the prefrontal cortex (Casey et al., 1996; Iadarola et al., 1998; Peyron et al., 2000; Ploghaus et al., 1999). Key prefrontal structures involved in the control of pain are the anterior cingulate cortex and insular cortex. Both regions express a high number of opioid receptor-positive neurons and project to the amygdala and PAG, two downstream structures mediating opioid-mediated analgesia and whose activation leads to a suppression of pain-related behavior and the subjective effects of pain. The prefrontal cortex is also hypothesized to control the midbrain-thalamic-cingulate nociceptive pathway though descending fibers (Lorenz et al., 2003).

Loss of Control Over Habits and Decision-Making—The concept of self-control in decision-making is a complex cognitive process that requires parallel analysis of multiple

sources of information, evaluation of outcomes, and selection of motor patterns. Loss of control in decision-making leads to unadapted behavior and is particularly prominent in situations with high incentives and high cognitive demand (George et al., 2008). Two key control mechanisms in decision-making are the ability to shift between different behavioral strategies, such as habit and goal-directed behavior, and attentional set-shifting to disengage from a once relevant stimulus dimension to a new set of stimuli that are potentially more relevant after a change in environmental conditions. The development of habit behavior is a particularly efficient strategy when environmental conditions do not change because habitual responses do not require evaluation of outcomes. Moreover, habit responses can be triggered by conditioned stimuli and require very limited cognitive resources, but inhibition of habits in favor of goal-directed behavior is critical when environmental conditions change to ensure adapted behaviors. A key structure mediating control over decision-making is the dorsolateral prefrontal cortex in humans and the dorsomedial prefrontal cortex in rodents (anterior cingulate cortex, prelimbic cortex; Dias-Ferreira et al., 2009; Hare et al., 2009; Birrell and Brown, 2000; Block et al., 2007; Dias et al., 1997; Ragozzino et al., 2003). Genetic variation at the serotonin transporter-linked polymorphism region has been associated with impaired amygdala control by the prefrontal cortex and may lead to poor decision-making (Roiser et al., 2009). Individual differences in the ability of the dorsolateral prefrontal cortex to modulate the ventromedial prefrontal cortex might be due to differences within the dorsolateral prefrontal cortex or to differences in connectivity between the dorsolateral prefrontal cortex and the subregions of the prefrontal cortex and the striatum. Particularly interesting for the control of decision-making is the fact that the prefrontal cortex contains a high number of GABAergic inhibitory interneurons and that pyramidal neurons can make both pyramidal-pyramidal connections and pyramidal-interneuron connections through extensive horizontal connections (Goldman-Rakic, 1995; Tanaka, 1999). Thus, pyramidal neurons can simultaneously activate and inactivate different corticocortical and corticostriatal circuits and facilitate behavioral flexibility by shifting attentional focus and selecting different motor patterns to adopt new strategies.

Conclusions

Important individual differences in the different stages of the addiction process, as well as in the vulnerability to the transition to addiction, have been observed in humans and animals. We reviewed studies demonstrating that the concept of self-regulation combined with the concept of modularity of cognitive function may help to understand individual differences in the vulnerability to drugs and to the transition to addiction. As explained above, there are important individual differences in the different stages of addiction as well as in key brain functions critical for the development of addiction, such as attention, decision-making, reward, emotion, pain, and stress (Crowley et al., 1998; de Wit et al., 1986; Deroche-Gamonet et al., 2004). Flexible, goal-directed behaviors require an adapted cognitive control system for organizing, selecting, and consolidating information resulting from the different modules into a coherent and unified experience (Treisman, 1996). Neuroanatomical, brain lesion, and site-specific pharmacological modulation studies of the prefrontal cortex have revealed the heterogeneity of the prefrontal cortex and the high functional specialization of its different subregions (Robbins, 2000). The prefrontal cortex and its different subregions target the main sources of all neurotransmitter systems and have been hypothesized to represent this cognitive control system (Baddeley, 1996; Robbins, 2000; Ridderinkhof et al., 2004, Goldman-Rakic, 1987).

We suggest that the concept of self-regulation, combined with the concept of modularity of cognitive function, may help to understand the neural basis of the individual differences in the vulnerability to drug addiction. Indeed, dysfunction of a specific subregion of the prefrontal cortex may lead to loss of control over a specific module, leading, for instance, to a sensitization of insentive salience in one individual and to a hyperreactivity of the stress system in another

individual. Therefore, the failure of a specific module may differ from one individual to another and may represent a neuropsychobiological mechanism underlying individual differences in the vulnerability to drug addiction.

Several key potential modules may be identified, including the incentive salience mesolimbic dopamine system module, stress/HPA axis module, habit/striatum module, negative emotional state/extended amygdala module, pain/spinothalamocortical module, and the decision-making/prefrontal cortex module. Such modules are driven by bottom-up signals from both the external world and interoceptive signals and by top-down signals from higher-order system mediating cognitive control. It is important to note that the modules described in this review do not correspond fully to the concept originally defined by Jerry Fodor (1983). One of the essential defining features of a Fodorian module is functional autonomy; that is, its function is little, if any, controlled by top-down cognitive control. In contrast, the brain systems identified here are hypothesized to be under tight top-down control by the prefrontal cortex, at least initially before the transition to addiction. These systems are not modular in the strong sense defined by Fodor but begin to resemble to Fodorian modules only after the transition to addiction.

The present multi-system framework may be useful to better understand the different patterns of drug addiction across different individuals and different drugs. It can be hypothesized that individuals with increased sensitivity of the incentive salience mesolimbic dopamine system module and the habit/striatum system may be particularly vulnerable to cocaine and methampetamine abuse through an overvaluation of drug reward and drug-related cues during the *binge/intoxication and preoccupation/anticipation* stages Wise 2002; Jentsch and Taylor 1999). Individual differences in the function of the incentive salience mesolimbic dopamine system and the habit/striatum modules may be particularly important for craving-type 1 (or reward craving) defined as craving for the rewarding effects of drugs and usually induced by stimuli that have been paired with drug self-administration such as environmental cues, as opposed to craving-type 2 (or withdrawal relief craving) which is conceptualized as an excessive motivation for the drug to obtain relief from a state change characterized by anxiety and dysphoria after protracted abstinence (Heinz et al., 2003). Individual differences in the pain/spinothalamocortical module may be key for the transition to opiate and alcohol dependence. Decreased sensitivity of the pain system is associated with a higher vulnerability for opiate dependence (Lehofer et al., 1997), whereas hyperactivity of the pain system may predict cue-induced craving in abstinent opiate abusers (Ren et al., 2009). Moreover, considering the importance of the endogenous opiate system in alcoholism, it is likely that vulnerability of the pain/spinothalamocortical or spinoparabrachial module (Besson, 1999) might be a risk factor for the development of alcoholism and dependence on other drugs (Herz, 1997). Hyperactivity of the negative emotional state/extended amygdala module is associated with increased emotional pain and stress and might be a risk factor for drug use as a self-medication for emotional pain, dysphoria, and stress (Khantzian et al., 1997). Vulnerability in the pain/spinothalamocortical module may lead to increased physical and emotional pain during withdrawal and intense craving-type 2, thus contributing to the preponderant role of the *withdrawal/negative affect* stage that characterizes opiate and alcohol addiction. Increased reactivity of the stress/HPA axis module may be critical in the initiation of drug intake and for the maintenance of drugs that have little initial rewarding value, such as nicotine, as it potentiates the reinforcing effects of drugs (Piazza and Le Moal, 1998). Vulnerability of the stress/HPA axis and the negative emotional state/extended amygdala module may contribute to the different patterns of tobacco smoking behavior. Indeed, individuals who smoke regularly but who will always limit their tobacco intake (“chippers”) show no signs of withdrawal and report less stress and better stress coping responses than subjects dependent on tobacco (Shiffman, 1989) suggesting that hyperaactivity of the stress/HPA axis and the negative emotional state/extended amygdala module may underlie the differences between chippers and dependent smokers. Finally, hypoactivity of the decision-making/prefrontal cortex module

may lead to a loss of control over drug intake despite negative consequence because of impaired inhibitory control and decision-making leading to choices of immediate rewards over delayed rewards (Goldstein and Volkow, 2002). Although the initial failure of a specific module might be specific to one stage of the addiction cycle and to a specific drug, in a given individual the transition to addiction is ultimately likely to be associated with a progressive and generalized loss of control over many, if not all, cognitive modules.

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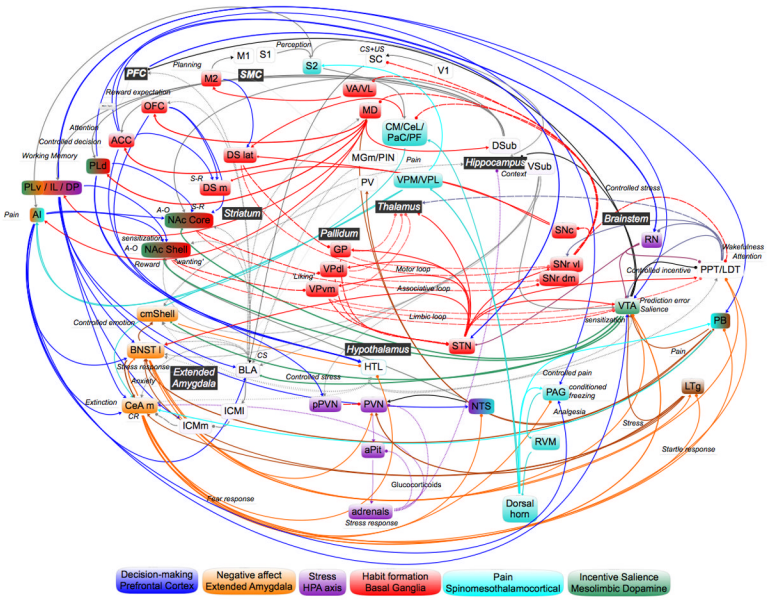

Figure 1. Anatomical functional differences in the prefrontal cortex in the rat

The prefrontal cortex in rats can be dissociated into medial, lateral, and ventral regions. The medial prefrontal cortex (PFC) is composed of a dorsal section with the anterior cingulate cortex (ACC), precentral cortex, and dorsal prelimbic cortex (PLd) and a ventral section with the ventral prelimbic (PLv), infralimbic (IL), dorsal peduncular (DP), and medial orbital (MO) cortices. The lateral PFC is composed of the lateral orbital (LO) and dorsolateral (DLO) cortices, the dorsal and ventral anterior insular cortices (AID, AIV), and the granular insular cortex (GI). The ventral PFC is composed of the ventral orbital (VO) and ventral lateral orbital (VLO) cortices. The prefrontal cortex can be subdivided into four main regions based on differential anatomical connections and functions: dorsal mPFC, ventral mPFC, OFC, and insula. It is important to note that these four regions are not homogeneous and can be further dissociated into subregions based on cellular architectonics and specific projections.

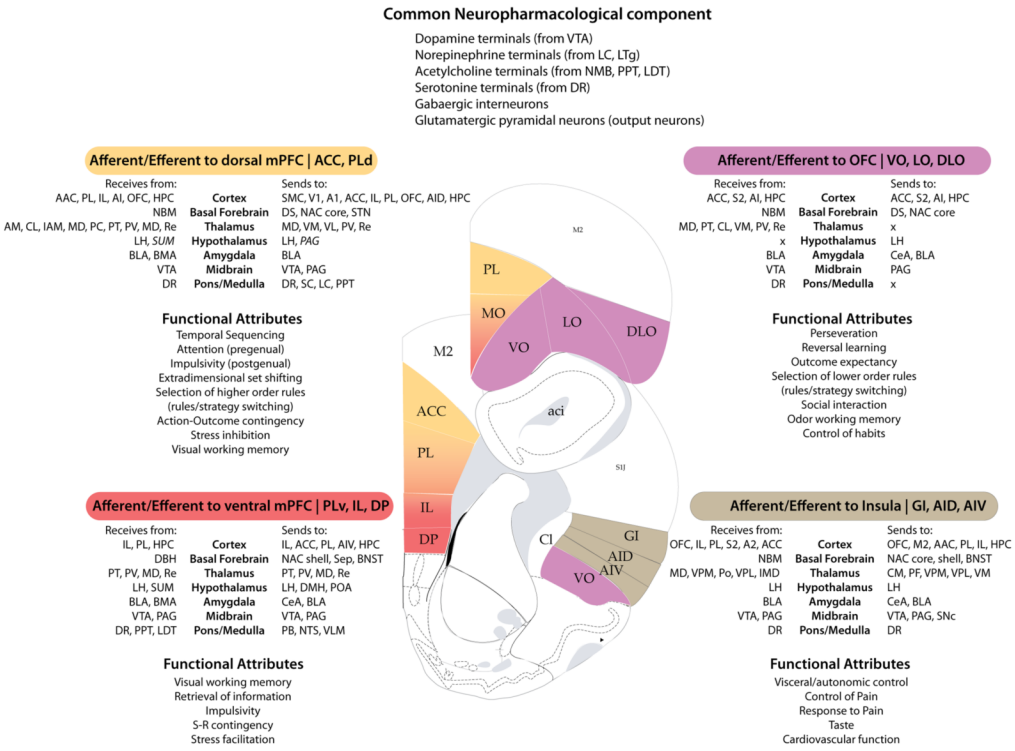

Figure 2. Neurocircuitry of addiction

Schematic representation of the prefrontal cortex and its connections with the different subcortical systems or modules mediating negative emotional states (orange), stress (red), pain (yellow), incentive salience (green), habits (beige), and decision-making (blue). The *incentive salience/mesolimbic dopamine system module* includes the dopamine neurons in the VTA projecting to the nucleus accumbens shell. Key processes are incentive salience, reward, and prediction error. The *decision-making/prefrontal cortex module* includes bidirectional connections of the PL, IL, AAC, and OFC. Key cognitive processes include working memory, reward evaluation and expectation, motor planning, and attention. The *habit/striatal module* receives and sends segregated connections with the prefrontal cortex and pallidum, respectively. Key processes in this module are action-outcome associations, reward (NAC shell, VP), expression of sensitization and conditioned reward (NAC shell), stimulus response associations, habits (NAC core and DS), approach behavior, retrieval and reconsolidation of drug associated memory (NAC core), and orienting and attention (DS). The *negative emotional state/extended amygdala module* represents a series of densely interconnected structures (CeA, BNST, NAC shell) with important connections with the brainstem, BLA, and hypothalamus. Key processes in the extended amygdala are the expression of conditioned responses, fear (CeA), the stress response, HPA control, negative emotional states, extinction of drug-seeking (CeA, BNST), stress-induced reinstatement (BNST), and autonomic responses (CeA, BNST). The *stress/HPA axis module* includes the PVN, aPit, and adrenals. Key processes include stress responses, immune suppression, energy storage and expenditure, and emotions. The *pain/spinothalamocortical module* includes the spinoreticulo-mesencephalo-thalamic tract, PB, PAG, RVM, VPL, CL, CM, PF, and CeA. Key processes include nociception, negative emotional state, pain expectancy (PAG, ACC), analgesia, and conditioned analgesia. These modules are interconnected but relatively independent in their functioning. Some structures are implicated in different modules, but it is important to note that segregated neuronal populations with different neuronal connections may be involved. Connections ending with an arrow are mainly excitatory, whereas connections with a dot are inhibitory. In many cases,

such as with the VTA and CeA, the prefrontal cortex connects with local interneurons (that are not represented) that change the excitatory connection to an inhibitory connection onto the output neurons of the given structure. Abbreviations: **Prefrontal cortex** (PFC): prelimbic cortex (PL), infralimbic cortex (IL), orbitofrontal (OFC), anterior cingulate cortex (ACC), dorsal peduncular cortex (DP), agranular insular cortex (AI). **Basal ganglia**: globus pallidus (GP), ventral pallidum (VP), dorsal striatum (DS), nucleus accumbens (NAC), subthalamic nucleus (STN), substantia nigra pars compacta (SNc), substantia nigra pars reticulata (SNr). **Hypothalamus**: suprachiasmatic nucleus (SCN), dorsomedial hypothalamus (DMH), perifornical area (PfA), lateral hypothalamus (HTL), paraventricular nucleus of the hypothalamus (PVN). **Extended amygdala**: central nucleus of the amygdala (CeA), bed nucleus of the stria terminalis (BNST), intercalated cell mass (ICM), basolateral amygdala (BLA). **Thalamus**: mediodorsal nucleus (MD), ventral anterior (VA) and ventral lateral (VL), centromedian (CM), central lateral (CeL), paracentral (PaC), parafascicular (PF), intermediodorsal (IMD), paraventricular (PV), ventroposteromedian (VPM), ventroposterolateral (VPL), medial geniculate nucleus (MGm), posterior intralaminar nucleus (PIN). **Brainstem**: ventral tegmental area (VTA), pedunculopontine tegmental nucleus (PPT), laterodorsal tegmental nucleus (LDTLTD), raphe nucleus (RN), lateral tegmental nucleus (LTg), parabrachial nucleus (PB), rostroventromedial medulla (RVM). **Other**: primary motor cortex (M1), secondary motor cortex (M2), primary somatosensory cortex (S1), secondary somatosensory cortex (S2), subiculum (Sub), superior colliculus (SC), inferior colliculus (IC), anterior pituitary (aPit).