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Unbalanced Neuronal Circuits in Addiction

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Abstract

Through sequential waves of drug-induced neurochemical stimulation, addiction co-opts the brain's neuronal circuits that mediate reward, motivation, , to behavioral inflexibility and a severe disruption of self-control and compulsive drug intake. Brain imaging technologies have allowed neuroscientists to map out the neural landscape of addiction in the human brain and to understand how drugs modify it.

Systems of circuits

Several theories have been put forward to explain the phenomenon of addiction. For example, unchecked impulsivity [1] (a failure to inhibit excessive drive), reward deficiency [2] (a blunted dopaminergic response to natural rewards), maladaptive learning [3] (the growing incentive salience of a drug's predictive cues with chronic use), the emergence of opponent processes [4] (the power of negative motivational states underlying withdrawal), faulty decision making [5] (inaccurate computation in preparation for action) or automaticity of responses [6] (inflexibility of stimulus-response habits), have all been the focus of intense and productive research. The fact is that that dysfunctions in these and many other functional modules [5] are likely to contribute, directly or indirectly, to an addicted individual's inability to suppress a maladaptive behavior in spite of its adverse consequences. The evidence suggests that the observable behaviors that characterize the addiction phenotype (compulsive drug consumption, impaired self-control and behavioral inflexibility) represent unbalanced interactions between complex networks (that form functional circuits) implicated in goal directed behaviors (Figure 1).

Several external perturbagens (e.g., drugs, food, gambling, sex, video games, high calorie foods, stress) can tip this balance (in vulnerable individuals) and trigger and addictive behavior. At the same time specific neural nodes and their associated networks, when dysfunctional (secondary to genetic or developmental deficits or from drug or other environmental exposures) can destabilize the interaction between brain circuits increasing the vulnerability for psychiatric disorders, including addiction. The molecular mechanisms that result in the improper communication between neuronal networks include changes in NMDA and AMPA receptor-mediated glutamate signaling [7], which will not be discussed here but have been reviewed elsewhere [8•]. The neural nodes, relays and connectivity

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patterns summarized in the following sections illustrate our current (and growing) understanding of the circuitry underlying addiction.

The Mesostriatocortical System

The ability to form habits has been a powerful and positive force in evolution. Compulsive behaviors, like addiction, can take hold when the neural circuitry that instantiates adaptive habits [9] is thrown off balance by exposure to drugs or other positive (food, sex, gambling) or negative reinforcers (stress) in vulnerable individuals [10]. The ability of certain behavioral routines to become deeply ingrained, after enough repetition, helps explain both the difficulty of suppressing them (i.e., compulsion [11–13]) and the ease with which they bounce back after extinction (i.e., relapse [14]). Habituation appears to be instantiated mainly in the mesostriatocortical circuits that “re-code” the behavioral fate of repetitive actions [14,15] in a process that was aptly referred to as the “chunking” of action repertoires [16•]. Schematic diagrams -at the anatomical and circuit levels- of the main frontocorticostratial pathways that contribute to reward-related habituation are presented (Figure 2A and B). Drug-induced adaptations anywhere along this bidirectional circuitry, between the ventral tegmental area (VTA) and the neighboring substantia nigra (SN), ventral and dorsal striatum, thalamus, amygdala, hippocampus, subthalamic nucleus and the prefrontal cortex (PFC) can trigger or facilitate the addictive process by disrupting reward-based learning via the modulation of regional neuronal excitability [17,18]. At the molecular level, such adaptations are the reflection of plastic changes that predominantly affect the way in which DA and glutamate neurotransmission become integrated, allowing for synapses to be strengthened or weakened as a result of interneuronal communication [19].

The DA system is a central cog in the mechanism that attributes saliency, hence its modulatory role in reward and reward prediction (expectation, conditioned learning, motivation (drive), emotional reactivity and executive functions. Many studies have established that DA signals emanating from the VTA/SN and arriving in the striatum play a pivotal role in learning from past experience and orchestrating appropriate behavioral responses. Whether directly or indirectly, all addictive drugs have the power to cause large and transient increases in DA from VTA neurons that project primarily into the Nucleus Accumbens (NAc) of the ventral striatum, but also to the dorsal striatum, amygdala, hippocampus and PFC [20] (Figure 2). Although not yet fully understood, we have made significant progress investigating the underlying processes.

A good example, at the molecular level, is the observation that the two principal classes of medium spiny neurons (MSN) in the striatum differ significantly in terms of their DA receptor patterns of expression: MSNs in the striatonigral (direct) pathway express D1 receptors (D1R), which drive enhanced dendritic excitability and glutamatergic signaling, whereas MSNs in the striatopallidal (indirect) pathway express D2 type receptors (D2R), which appear to mediate the opposite effect [21•]. These differences impact the neurotransmission patterns that influence reward-processing behaviors on the basis of whether or not an expected reward had actually been obtained (Figure 3). For drug reward, studies have shown that an imbalance between D1R (drug-dependently enhanced) and D2R (drug-dependently decreased) signaling facilitates compulsive drug intake [22,23]. For example, administration of antagonists that specifically block either the direct (D1; SCH23390) or indirect (D2; Sulpiride) pathways in the dorsomedial striatum have opposite effects on a task that measures behavioral inhibition, with the former decreasing Stop Signal Reaction Time but having little effect on the Go response, and the latter increasing both Stop Signal Reaction and Go Trial Reaction times [24]. These results suggest that the differential expression of DA receptors in the dorsomedial striatum enables a balanced behavioral inhibition independently of behavioral activation. Interestingly, D1R have low affinity for

DA and hence they are active when exposed to large DA increases as occurring during intoxication whereas D2R are high affinity and hence stimulated not just by sharp DA increases but also by the relatively lower levels conveyed by tonic DA levels. Thus, effects of drugs are likely to have shorter duration of action in D1R mediated signaling than in D2R signaling, which was recently corroborated for cocaine's effects in striatal's MSN [23]. Stimulation of D1R is necessary for conditioning including that triggered by drugs [25]. The effects of repeated drug exposure in animal models implicate sensitization of D1R signaling whereas both preclinical and clinical studies document decreases in D2R signaling [26,27]. This leads to what appears to be an imbalance between the stimulatory direct D1R mediated striatocortical pathway and the inhibitory D2R mediated indirect pathway. A third, so called hyperdirect pathway, has also been described (also depicted in Figure 2B), in which excitatory projections between the inferior frontal gyrus (IFG) and the subthalamic nuclei (from motor related cortical areas into the globus pallidus) cause thalamic inhibition at a faster speed relative to the direct or indirect pathways, and it has been implicated in the ability to suppress a behavior after it has been initiated [28].

A better understanding of the biological and environmental forces that shape the mesostriatocortical circuits is bound to translate into more effective interventions. For example, maternal stress has been shown to negatively affect the dendritic arborization in the NAc and in prefrontocortical structures of the developing fetus [29•]. Similarly children reared in orphanages show underdeveloped frontal connectivity [30••]. Because of the central position of the NAc in the circuit that translates motivational inputs from the limbic system into goal-directed behaviors, and its connectivity with the PFC, which is necessary for self-control, these findings could help explain the association between early adverse events, brain development trajectories, and mental health [31–33].

Similarly, our better understanding of mesostriatocortical circuits has also started to shed light into the neurobiological processes that underlie the inverse relationship between age of initial drug use and addiction risk [34]. For example, the change from a predominant influence of the SN as the source of DA connectivity to subcortical and cortical regions in childhood/adolescence to a combined influence of the SN and the VTA in young adulthood [35•] could make this transition period particularly sensitive to the increased vulnerability to substance use and other psychiatric disorders, observed early in life. The discovery of this maturational effect suggests important new research questions. For example, could this connectivity shift modulate the regulatory impact of the corticotropin releasing factor binding protein (CRF-BP), a modulatory factor that can potentiate glutamatergic responses [36] implicated in reinstatement of cocaine seeking [37], and that is expressed in VTA but not in SN [38]?

Limbic Hubs

The core mesostriatocortical circuitry outlined above interacts with other structures in the limbic system that influence reward-related behaviors by providing information related to, among others, emotional valence, stored memories, sexual and endocrine function, autonomic control, interoception, and energy homeostasis. Below, we highlight key recent findings pertaining to the involvement of some of these nodes in substance use disorders (SUDs).

Amygdala

The amygdala encodes loss aversion and injects emotion and fear in the decision-making process. It also appears to act in concert with the ventral striatum to pick up stimuli that are not just emotionally *salient* but highly *relevant* to a task-dependent reward [39]. The extended amygdala (central nucleus of the amygdala, bed nucleus of the stria terminalis, and

NAc shell), through increased signaling via the corticotropin-releasing factor (CRF) and CRF-related peptides, is also involved in stress responses and contributes (but see also the case for the habenula, below) to a broader *anti-reward system* [40••]. The amygdala is a powerful modulator of addictive behaviors, especially during the protracted incubation of cue-induced drug cravings [41]. The basolateral amygdala (BLA) receives dopaminergic innervations from the VTA and expresses D1 and D2 receptors, which differentially influence the modulation of NAc and PFC function by the BLA. For example, intra-BLA administration of a D1R antagonist potentiates stress-induced DA release in NAc while attenuating it in medial PFC (mPFC) whereas a D2R antagonist had no effect on these regions [42]. It should be added that D3 type receptors in the central amygdala also play a role in the incubation of cocaine craving [43••]. Not surprisingly, there is some evidence to suggest that deep brain stimulation of the amygdala could help in the treatment of various mental disorders, including addiction [44•].

Insula

The transition from flexible, goal directed to reflexive, compulsive behaviors appears to also be influenced by instrumental learning as modulated by interoceptive and exteroceptive inputs. The insula plays a major interoceptive role by sensing and integrating information about the internal physiological state (in the context of ongoing activity) and conveying it to the anterior cingulate cortex (ACC), ventral striatum (VS), and ventral medial PFC (vmPFC) to initiate adaptive behaviors [45]. Consistent with its role in bridging changes in internal state and cognitive and affective processing, neuroimaging studies have revealed that the middle insula plays a critical role in cravings for food, cocaine and cigarettes [46–48] and on how an individual handles drug withdrawal symptoms. Thus, insular dysfunction is associated with drug craving in addiction [49], a notion that is supported by the documented ease with which smokers who had suffered insular damage were able to quit [50••], as well as by several imaging studies of addicted individuals [51,52]. The observed associations between alcohol and insular hypofunction [53], and between heroin and cocaine use and gray insular matter deficits relative to controls [54], may also account for the deficits in self-awareness during intoxication and the failure to recognize the pathological state of addiction by the addicted individual, which has been traditionally ascribed to denial [55]. [55]. In fact, many imaging studies show differential activation of the insula during craving [56], which has been suggested to serve as a biomarker to predict relapse [57].

Thalamus, subthalamic nucleus (STN), epithalamus

Chronic drug abuse eventually impinges on the connectivity of critical hubs [58]. For example, cocaine abusers, compared to controls, present lower functional connectivity between midbrain (location of SN and VTA) and thalamus, cerebellum, and rostral ACC, which is associated with reduced activation in thalamus and cerebellum and enhanced deactivation in rostral ACC [59]. The performance of these hubs, and their multiple targets, can be perturbed not just by chronic but also by acute exposure to drugs of abuse: for example, alcohol intoxication can cause a fuel switch, from glucose to acetate, in the thalamus, cerebellum and occipital cortex and this switch is facilitated with chronic alcohol exposures [60•]. On the other hand, a recent study of 15 treatment-seeking cocaine-addicted individuals found that just 6 months of abstinence could rescue much of the reduced neural activity in midbrain (encompassing VTA/SN) and thalamus (encompassing the mediodorsal nucleus), which reduced cocaine seeking behavior as simulated in a drug word choice task [61••].

The STN plays a vital role in the integration of limbic and associative information in preparation for its transmission towards cortical and subcortical regions [62]. It regulates motor action and is involved in decision making particularly when engaging in difficult

choice decisions [63,64]. Several studies have implicated the STN in addiction. One report, for example, found that the robust crosstalk between impulse control and cognitive processing that improves substance use outcomes and contributes to adolescent resiliency hinges heavily on STN performance [65]. Deep brain stimulation of the STN, which is used in the treatment of Parkinson's [66] and might be useful in severe OCD [67] has been tested in preclinical studies to reduce the sensitized responses to cocaine-cues [68].

DA signaling from VTA and SN is critical for learning approach behaviors from reward whereas inhibition of VTA DA signaling by the lateral habenula enables learning avoiding behaviors when an expected reward does not materialize [69] or when an aversive stimulus or negative feedback is provided [70]. Thus, the lateral habenula together with amygdala/stress system may constitute part of an anti-reward circuitry in the brain that negatively motivates behaviors. This is consistent with the results of a preclinical study in which activation of the lateral habenula triggered relapse to cocaine and heroin self-administration [71,72]. Current thinking then posits that chronic use of addictive drugs leads to habenular hyperactivity, which promotes a negative emotional state during drug withdrawal [73].

Cerebellum

Convergent studies are also implicating the cerebellum, and the cerebellar vermis in particular, in addiction. For example, the cerebellum, along with the occipital cortex and thalamus is one of the brain areas that undergoes the steepest activation in response to intravenous methylphenidate [74••] and, like in the thalamus, the effect in the vermis was significantly amplified (~50%) whenever methylphenidate was expected by cocaine abusers, suggesting its involvement in expectation of drug reinforcement [74••]. Indeed, other studies have found that cocaine cues can trigger the activation of cerebellar vermis in cocaine users [75], and that vermis activation was associated with abstinence in alcohol addiction [76]. A likely contribution of the cerebellum to the addiction process is also suggested by imaging studies implicating it in cognitive processes underlying the execution of goal-directed behaviors and their inhibition when they are perceived as disadvantageous [75•].

The dopamine content in cerebellum is low so it had not been traditionally considered as part of the circuitry modulated by DA [77]. However, the primate cerebellar vermis (lobules II–III and VIII–IX) displays significant axonal dopamine transporter immunoreactivity, which, together with the existence of VTA projections to the cerebellum suggests that a reciprocal midbrain to cerebellum circuit is likely [78]. The relevance of VTA-cerebellar vermis communication to reward processing is also supported by independent human fMRI based observations of correlated neural activity in VTA and cerebellar vermis while viewing faces of the opposite sex [79] and of strong functional connectivity between VTA and SV and the cerebellar vermis (Tomasi and Volkow, in press).

Frontocortical Substrates

Much of early addiction research focused on limbic brain areas because of their role in drug reward [80]. However, the drug-induced DA boost, does not explain addiction since it happens in naïve animals and its magnitude is decreased in addiction [81•]. In contrast, preclinical and clinical studies are revealing neuroadaptations in PFC that are uniquely activated by the drug or drug cues in addicted but not in non-addicted individuals and are therefore likely to play a key role in the addiction phenotype (for review, see [82]).

In humans addicted to drugs, the reduction in striatal D2R, which is implicated in some impulsive and compulsive behavioral phenotypes [83], is associated with decreased activity of PFC regions, including orbitofrontal cortex (OFC), ACC, and dorsolateral prefrontal cortex (DLPFC) [84–86]. Studies have also shown, decreased frontal cortical activity during

intoxication for many of the drugs of abuse [87] that remains after drug discontinuation in chronic abusers [88]. Indeed, disruption of several frontocortical processes has been reported in chronic drug users (Table I) (see [13] for a review). Naturally, targeting the frontal impairments in addiction has been a holy grail of therapeutic strategies to improve self-control [61] [89].

Among the frontal regions implicated in addiction the OFC, ACC, DLPFC and inferior frontal gyrus (IFG; Brodmann area 44) stand out because of their participation in salience attribution, inhibitory control/emotion regulation, decision making and behavioral inhibition respectively (Figure 2B). It has been postulated that their improper regulation by D2R-mediated striatal DA signaling in addicted subjects could underlie the enhanced motivational value of drugs and the loss of control over drug intake [90••]. Incidentally, related dysfunctions could also underlie some behavioral addictions, like pathological internet use [91] and compulsive food intake in some forms of obesity [83]. Interestingly, and echoing a recurring theme, investigators have also found evidence of differential roles for D1R and D2R in the PFC. For example, recent preclinical studies have shown that pharmacologic blockade of mPFC D1R attenuates; whereas D2R increases a tendency for risky choices, providing evidence for a dissociable but complementary role of mPFC DA receptors that is likely to play a major role in orchestrating the fine balance needed for inhibitory control, delayed discounting, and judgment [92].

In addition, because impairments in OFC and ACC are associated with compulsive behaviors and impulsivity, DA's impaired modulation of these regions is likely to contribute to the compulsive and impulsive drug intake seen in addiction [93]. Clearly, low DA tone could just as well constitute a preexisting vulnerability for drug use in PFC, albeit one that is likely to be exacerbated with the further decreases in striatal D2R triggered by repeated drug use. Indeed, a study performed in subjects who, despite a positive family history (high risk) of alcoholism, were not themselves alcoholics, revealed a higher than normal striatal D2R availability that was associated with normal metabolism in OFC, ACC, and DLPFC [94•]. This suggests that, in these subjects at risk for alcoholism, the normal PFC function was linked to enhanced striatal D2R signaling, which in turn may have protected them from alcohol abuse.

Also suggestive of compensatory mechanisms that could afford protection to some members of an at-risk family, a recent study of siblings discordant for their addiction to stimulant drugs [95••] showed brain differences in the morphology of their OFC, which were significantly smaller in the addicted sibling than in controls, whereas in the non-addicted siblings the OFC did not differ from that of controls [96].

Treatment implications

Increasing our understanding of the neural systems affected by chronic drug use as well as the modulatory impact that genes in conjunction with developmental and environmental forces have on these neuronal processes, will improve our ability to design more effective strategies for prevention and treatment of SUD.

Irrespective of whether or which of the addiction-related impairments highlighted in this review lead to or follow chronic drug use, the combined multidisciplinary evidence suggests the existence of multiple neuronal circuits that become dysfunctional with addiction and that could be targeted more precisely through pharmacological, physical, or behavioral means to attempt and mitigate, halt, or even reverse a specific deficit. For example, functional MRI studies show that oral methylphenidate can normalize activity in two major ACC subdivisions (i.e., the caudal-dorsal and the rostroventromedial) and decrease impulsivity in cocaine addicted individuals during an emotionally salient cognitive task [97•]. Similarly, a

better understanding of the main nodes within circuits disrupted by addiction offers potential targets for investigating the value of transcranial magnetic stimulation (TMS) or even deep brain stimulation (DBS) in treatment-refractory patients suffering from addiction [98•]. Finally, evidence-based psychosocial interventions are becoming more effective and available for the treatment of SUDs, a trend that is likely to accelerate thanks to the development and deployment of novel approaches enhanced by digital, virtual, and mobile technologies [99], and by our expanded understanding of the social brain, which will allow us to take advantage of the powerful influence of social factors in modulating neuronal circuits and human behaviors [100].

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Highlights

- Addiction is a spectrum disorder that perturbs the balance within a network of circuits.
- Addiction entails a progressive dysfunction that erodes the foundations of self-control.
- Addiction circuits overlap with the circuits of other impulsivity disorders (e.g., obesity).
- Better understanding of these circuits is the key to better prevention and treatment.

Figure 1.

A carefully balance set of interconnected functional modules instantiates the processing of myriad and competing signals, including reward, expectation, saliency, motivation, value learning, emotional value, ambiguity, conflict, and cognitive processing that underlie decision making and ultimately our ability to exert free will. Many extrinsic and intrinsic factors (triggers), acting upon a variety of intermediary systems (mediators), can perturb the balance among the system of circuits in charge of orchestrating adaptive goal directed behaviors.

Figure 2.

Fronto-striatal circuitry of stimulus-response habits. **A.** Schematic anatomical representation of the mesocorticolimbic dopamine system in the human brain, highlighting several key processing stations: Ventral Tegmental Area (VTA) and Substantia Nigra (SN), Nucleus Accumbens (NAc) in the ventral striatum, Thalamus and Subthalamic Nuclei, and Prefrontal cortex, among others. Modified with permission [15]. **B.** Four of the frontostriatal cortical circuits that appear to play major roles in executive functioning and inhibitory control. DL: dorsolateral; DM: dorsomedial; VA: ventroanterior; VM: ventromedial; r: right; IFG: inferior frontal gyrus; preSMA: pre somatic motor area; STN: sub-thalamic nucleus. Modified with permission [28].

Figure 3.

Schematic depiction of dopaminergic control of positive and negative motivation loops in the dorsal striatum. **A.** When an action results in a better-than-predicted situation, DA neurons fire a burst of spikes, which is likely to activate D1Rs on direct pathway neurons and facilitate immediate action and corticostriatal plasticity changes that make it more likely to select that action in the future. **B.** In contrast, when the result of an action is worse-than-expected, DA neurons are inhibited reducing DA, which is likely to inhibit D2Rs indirect pathway neurons, suppressing immediate action and the reinforcement of corticostriatal synapses, leading to suppression of that action in the future. Reprinted with permission [101].

Table 1
Processes associated with the prefrontal cortex that are disrupted in addiction

Orbitofrontal cortex (OFC) includes Brodmann area (BA) 10–14 and 47, and inferior and subgenual regions of anterior cingulate cortex (ACC) (BA 24, 25 and 32) in the ventromedial prefrontal cortex (vmPFC); ACC includes rostral ACC (rACC) and dorsal ACC (dACC) (BA 24 and 32, respectively), which are included within the medial PFC (mPFC). The mPFC also includes BA 6, 8, 9 and 10; dorsolateral PFC (DLPFC) includes BA 6, 8, 9 and 46; and the inferior frontal gyrus (IFG) and ventrolateral PFC (vIPFC) includes inferior portions of BA 8, 44 and 45. These various processes and regions participate to a different degree in craving, intoxication, bingeing and withdrawal. IOFC, lateral OFC; mOFC, medial OFC; PFC, prefrontal cortex. Reprinted with permission [13].

Process	Possible disruption in addiction	Probable PFC region
Self-control and behavioural monitoring: response inhibition, behavioural coordination, conflict and error prediction, detection and resolution	Impulsivity, compulsivity, risk taking and impaired self-monitoring (habitual, automatic, stimulus-driven and inflexible behavioural patterns)	DLPFC, dACC, IFG and vIPFC
Emotion regulation: cognitive and affective suppression of emotion	Enhanced stress reactivity and inability to suppress emotional intensity (for example, anxiety and negative affect)	mOFC, vmPFC and subgenual ACC
Motivation: drive, initiative, persistence and effort towards the pursuit of goals	Enhanced motivation to procure drugs but decreased motivation for other goals, and compromised purposefulness and effort	OFC, ACC, vmPFC and DLPFC
Awareness and interception: feeling one's own bodily and subjective state, insight	Reduced satiety, 'denial' of illness or need for treatment, and externally oriented thinking	rACC and dACC, mPFC, OFC and vIPFC
Attention and flexibility: set formation and maintenance versus set-shifting, and task switching	Attention bias towards drug-related stimuli and away from other stimuli and reinforcers, and inflexibility in goals to procure the drug	DLPFC, ACC, IFG and vIPFC
Working memory: short-term memory enabling the construction of representations and guidance of action	Formation of memory that is biased towards drug-related stimuli and away from alternatives	DLPFC
Learning and memory: stimulus–response associative learning, reversal learning, extinction, reward devaluation, latent inhibition (suppression of information) and long-term memory	Drug conditioning and disrupted ability to update the reward value of non-drug reinforcers	DLPFC, OFC and ACC
Decision making: valuation (coding reinforcers) versus choice, expected outcome, probability estimation, planning and goal formation	Drug-related anticipation, choice of immediate reward over delayed gratification, discounting of future consequences, and inaccurate predictions or action planning	IOFC, mOFC, vmPFC and DLPFC
Salience attribution: affective value appraisal, incentive salience and subjective utility (alternative outcomes)	Drugs and drug cues have a sensitized value, non-drug reinforcers are devalued and gradients are not perceived, and negative prediction error (actual experience worse than expected)	mOFC and vmPFC

Orbitofrontal cortex (OFC) includes Brodmann area (BA) 10–14 and 47 (REF. 216), and inferior and subgenual regions of anterior cingulate cortex (ACC) (BA 24, 25 and 32) in the ventromedial prefrontal cortex (vmPFC)³³⁷: ACC includes rostral ACC (rACC) and dorsal ACC (dACC) (BA 24 and 32, respectively), which are included within the medial PFC (mPFC). The mPFC also includes BA 6, 8, 9 and 10 (REF. 218); dorsolateral PFC (DLPFC) includes BA 6, 8, 9 and 46 (REF. 219); and the inferior frontal gyrus (IFG) and ventrolateral PFC (vIPFC) encompass inferior portions of BA 8, 44 and 45 (REF. 220). These various processes and regions participate to a different degree in craving, intoxication, bingeing and withdrawal. IOFC, lateral OFC; mOFC, medial OFC; PFC, prefrontal cortex.