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A neurocognitive approach to understanding the neurobiology of addiction

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Recent concepts of addiction to drugs (e.g. cocaine) and non-drugs (e.g. gambling) have proposed that these behaviors are the product of an imbalance between three separate, but interacting, neural systems: an impulsive, largely amygdala–striatum dependent, neural system that promotes automatic, habitual and salient behaviors; a reflective, mainly prefrontal cortex dependent, neural system for decision-making, forecasting the future consequences of a behavior, and inhibitory control; and the insula that integrates interoception states into conscious feelings and into decision-making processes that are involved in uncertain risk and reward. These systems account for poor decision-making (i.e. prioritizing short-term consequences of a decisional option) leading to more elevated addiction risk and relapse. This article provides neural evidence for this three-systems neural model of addiction.

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Introduction

Once an individual has lost control over drug use or nondrug use behaviors, rising negative consequences (e.g. financial problems) do not lead to necessary behavioral adjustments (e.g. regulate or quit drinking or gambling) [1]. Because of vulnerability mechanisms and/or to toxic effect of drugs, this state of 'inflexibility' has been thought to reflect impaired 'basic' behavioral learning processes, poor self-regulation and impaired decision-making. In order to unify vision of addiction that integrates both experimental and clinical perspectives, we propose here that drug and behavioral addictions are associated with disrupted neural systems for willpower, which refers to the capacity for choosing according to long-term, rather than short-term, outcomes. This disruption may occur in any one or a combination of three key neural systems: a hyperactive impulsive, amygdala–striatum dependent, neural system that promotes automatic and habitual actions; a hypoactive reflective, prefrontal cortex dependent, neural system for decision-making, forecasting the future consequences of a behavior, inhibitory control, and self-awareness; and an insula mediated neural system, which translates bottom-up, interoceptive signals into subjective output (e.g. craving), which in turn potentiates the activity of the impulsive system, and/or weakens or hijacks the goal-driven cognitive resources needed for the normal operation of the reflective system. At the process level, the characteristics of the impulsive and reflective neural systems mirror dual-processing accounts; one fast, automatic, and unconscious and the other slow, deliberative and conscious [2,3,4]. The insula is viewed as a 'gate' system that responds to homeostatic perturbations [5], which in turn modulate activities of the dual systems [6]. The main purpose of this article is to highlight the key role of choice in addiction, and to present a broad conceptual framework that brings together several disparate lines of research on addiction.

The impulsive system

Over the course of the development of an addiction, related behaviors become progressively controlled by addiction-associated information that have acquired, through Pavlovian and instrumental leaning mechanisms, the property to automatically generate drug-related (or gambling) actions and craving [7,8]. These fast and poorly deliberated responses triggered by competent cues (e.g. affects, a bottle of beer) present in the environment intimately depend upon basal ganglia and their cortical inputs [9]. Critically, the amygdala–striatal (dopamine dependent) neural system is a key structure for the incentive motivational effects of a variety of non-natural rewards (e.g. psychoactive drugs) and natural rewards (e.g. food) [10]. This stimulus bound rigid and automatic habit decision making system, which does not require mental simulation [11], is modified by abused substances through changes in the phasic characteristics of dopamine activity in reward signaling and the tonic function of dopamine levels in permitting and facilitating a large variety of motor and cognitive functions [12,13]. Increased mesolimbic dopamine activity, stimulated by drugs of abuse, reinforces the repetition of behaviors, influencing learning, attentional processes, and the strengthening of associations of reinforcing effects [14–16]. Through intensive practice and operant conditioning

processes, instrumental performance (e.g. a rat pressing a lever to receive cocaine) could easily switch from goal-directed action-outcome associations, which requires a representation of the outcome as a goal, to actions more independent of the current value of the goal [17], thus characterizing a state of compulsivity [18]. The transition between goal-directed and compulsive behaviors was associated with specific aspects of synaptic structural plasticity in both dorsal [19,20••,21] and ventral striatal regions [20••] and this process is accelerated by the sensitization of dopaminergic systems [22]. At the cognitive processing level, continued drug use results in the strengthening of implicit 'wanting' motivation-relevant associative memories [16], addiction-related cues are flagged as salient and grab the addicts' attention [23] and generate automatic approach tendencies [16]. These cognitive aspects are coherent with the incentive sensitization theory [8,24] which suggests that, through repetition of rewarding appetitive experiences, the degree to which addiction-related objects are 'wanted', desired and their effect anticipated, increases disproportionately when compared with the degree to which they are 'liked' (i.e. the actual mood change), and that this dissociation may progressively increase with the development of addiction [8,24].

In addition to the increased salience attribution to cues that predict drug reward, addiction is characterized by a decreased sensitivity to natural rewards [25,26••] as seen for instance in cocaine abusers for whom rewards that are not cocaine-related would generate below normal mesocorticolimbic neural activations, such as in response to monetary reward [27]. Taken together, all this ascribes a functional role to the striatum/amygdala complex in the automatic motivational and behavioral aspects of drug seeking.

The reflective system

While the habit (or impulsive) system, which is key to generating at least the 'wanting' component to seek reward, may explain one important aspect of the behaviors associated with approach behaviors, it is clear that it does not explain how one does control his or her behavior. This function refers to the action of the so-called 'reflective system', which is necessary to control these more basic impulses and allow more flexible pursuit of long-term goals.

The action of the reflective system depends on the integrity of two sets of neural systems: a 'cool' and hot' executive functions system [28], although in a normally functioning brain, it is very difficult to separate the 'cool' from the 'hot' functions, and whenever this separation occurs, the end result is a behavior resembling that associated with ventromedial prefrontal cortex damage or psychopathic/antisocial behavior [29]. 'Cool' executive functions are mediated by lateral inferior and dorsolateral frontostriatal and frontoparietal networks [30] and refers to basic working memory operations such as the maintenance and updating of relevant information ('updating'), inhibition of prepotent impulses ('inhibition'), and mental set shifting ('shifting') [31]. 'Hot' executive functions are mediated by paralimbic orbitomedial and ventromedial frontolimbic structures involved in triggering somatic states from memories, knowledge, and cognition, which allow to activate numerous affective/emotional (somatic) responses that conflict with each other; the end result is that an overall positive or negative signal emerges [32]. Thus, adequate decision-making reflects an integration of cognitive (i.e. 'cool' executive functions) and affective (i.e. 'hot' executive functions) systems, and the ability to more optimally weigh short term gains against long term losses or probable outcomes of an action [33].

Disrupted function in the 'reflective' prefrontal cortex could lead to impaired response inhibition and abnormal salience attribution in addiction, which provides an explanation of why drug seeking and taking become a main motivational drive at the expense of non-drug activities [1]. By compromising self-regulation in different ways [34], 'cool' executive functions deficits affecting drug and gambling addicted persons [35] are thought to accelerate the course of addiction by compromising abstinence from cocaine [36], gambling [37], nicotine [38], alcohol [39], and aggravating problem gambling [40•], and by increasing attrition from treatment [41]. The impact of 'hot' executive processes in addiction has been initially demonstrated in clinical research with patient populations with damage in frontal lobe regions as well as imaging studies that delineate the likely neural basis of each of these functions [32,42]. After damage to the ventromedial region of the prefrontal cortex, previously well-adapted individuals become unable to observe social conventions and decide advantageously on personal matters [43]. The nature of these deficits revealed that the vmPFC region serves as a link between a certain category of event based on memory records in high order association cortices and effector structures that produce an emotional response [42]. Damage to the systems that impact emotion and/or memory compromise the ability to make advantageous decisions [43]. The Iowa Gambling Task (IGT) [44], which was initially developed to investigate the decision-making defects of neurological patients in real-life has been shown to tap into aspects of decision-making that are influenced by affect and emotion [42]. The IGT detects decreased decision performance in persons with a variety of addictions in comparison with non-problematic control groups [45]. For instance, in some adolescents, poor decision-making confirmed by the IGT may predate the onset of alcohol use problems [46].

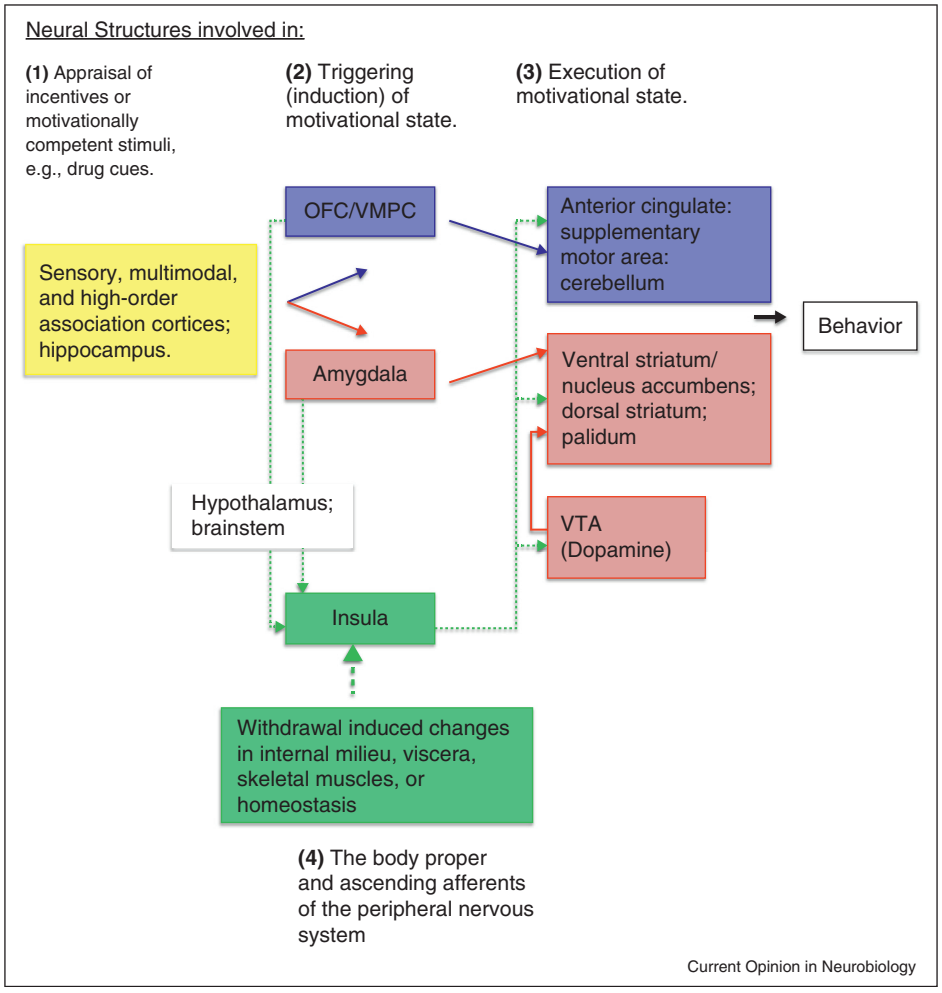
Neural systems that intensify motivation and weaken control of behavior: the insula

The insular cortex has recently emerged as a key neural structure that plays a key role in the formation of interoceptive representation, which is crucial for subjective emotional feelings [5,6,47]. Moreover, it has recently been argued that the insular cortex may contribute to the onset and maintenance of addiction by translating interoceptive signals into what one subjectively experiences as a feeling of desire, anticipation, or urge [6,48••]. Imaging studies confirmed activity within the insula correlating with the subjects' rating or urge for cigarettes, cocaine, alcohol and heroine [5,6,48••]. Strokes that damage the insular tend to literally wipe out the urge to smoke in individuals previously addicted to cigarette smoking [49]. In this study, smokers with brain damage involving the insula were >100 times more likely than smokers with brain damage not involving the insula to undergo a 'disruption of smoking addiction', which is characterized by the ability to quit smoking easily and immediately, without relapse, and without a persistence of the urge to smoke [49]. These results support a novel conceptualization of one of the mechanisms by which the insula participates in maintaining addiction (see Figure 1).

The insular cortex (and most likely the anterior insula) responds to interoceptive signals (due to homeostatic imbalance, deprivation state, stress, sleep deprivation, etc.). Besides the translation of these interoceptive signals into what may become subjectively experienced as a feeling of 'urge' or 'craving', we hypothesize that the insular cortex activity increases the drive and motivation to smoke (or take drugs or to gamble) by sensitizing or exacerbating the activity of the habit/impulsive system; and by subverting the mechanisms of the PFC for attention, reasoning, planning, and decision-making processes, which are necessary to formulate plans for action to seek and procure cigarettes or drugs [50••]. Put differently, these interoceptive representations have the capacity to 'hijack' the cognitive resources necessary for exerting inhibitory control to resist the temptation to smoke or use drugs by disabling (or 'hijacking') activity of the prefrontal (control/reflective) system. Although empirical evidence is still needed in support of this hypothesis, there are a number of structural and functional brain imaging studies that support this perspective. First, the anterior insula has bidirectional connections to, among others, the amygdala, ventral striatum and orbito-frontal cortex, and it has been argued that the homeostatic imbalance associated with certain psychological states (e.g. anxiety and stress) sends interoceptive signals that are received by the insula, which in turn exert influence on other neural systems [51]. Second, some studies have shown that drug cues disrupt top down control through deactivation of brain regions that are components of a frontal–parietal, and cingulate-opercular networks [52•], which are also parts of what we have described as the reflective system. In addition, drug cues elicit increased brain activation in regions involved in attribution of incentive salience (posterior regions of the mesial orbito-frontal cortex and ventral striatum, which is a part of what we described as the impulsive system), and deactivation in regions between the prefrontal cortex and the precuneus implicated in the motivation to make a certain decision (which are parts of what we referred to as the reflective system) [53]. However it remains unclear whether this activation is also associated with a craving or an urge to use drugs, and mediated through the insula [54]. Finally, similar to individuals experiencing chronic stress [55], repeated episodes of craving also result in structural reorganization of corticostriatal circuits (e.g. atrophy of the associative corticostriatal circuits and hypertrophy of the circuits coursing through the sensorimotor striatum), which could make decision-making mostly driven by habitual strategies. All these findings provide preliminary support for our proposed mechanism on the interaction of the insula with the impulsive and reflective neural systems. Nonetheless, more empirical studies are still needed, and this research should provide a promising new avenue for understanding poor decision-making in addicted persons.

Recent theoretical accounts [26••,56] advance that a dysfunction of the interoceptive system may also hamper self-awareness, which could take the form of failure to recognize an illness (i.e. lack of insight). Indeed, perceived need for treatment concerns only a minority of individuals suffering from addiction [57], which might reflect dysfunction in cognitive processes and the neural circuits underlying self-awareness [56]. The underestimation of the addiction severity might drive these individuals' excessive drug use, where control of use becomes exceedingly deregulated. Impaired insight ability could be estimated through the evaluation of metacognition capacity, which refers to as our ability to discriminate correct from incorrect performance. Dissociations between self-perception and actual behavior in addiction have been found in cocaine users [26••,58], in individuals with alcohol [59], with nicotine dependence [60], in methamphetamine-dependent subjects [61] and young marijuana abusers [62], as well as in pathological gamblers [63•], and it was found to have an impact on the capacity to remain abstinent, for instance, from alcohol [64]. This abnormal degree of dissociation found in addicted people between the 'object' level and the 'meta' level raised the possibility that poor metacognition leads to poor action and decision making monitoring and adjustment [65]. However, much remains to be done in order to identify how rostral and dorsal prefrontal cortex neural systems interact with interoceptive signals to promote accurate judgment performance, and to further enhance cognitive control of decision-making, memory, as well as one's sense of

Figure 1



A schematic neurological model illustrating a proposed functional role for three key neural systems in addiction: **(1)** the amygdala–striatal neural system, which we have termed the 'impulsive system', excites the traditional reward system involved in the execution of motivational states to seek drugs, such as the ventral striatum/nucleus accumbens and the mesolimbic dopamine system (highlighted in red); **(2)** the mesial orbitofrontal/ ventromedial prefrontal cortex (OFC/VMPC) is a key structure in a neural system we have termed the 'reflective system', which forecasts the future consequences of a behavior such as seeking drugs; **(3)** the proposed functional role of the insula is highlighted in green. Incentive stimuli (e.g. drug cues) generate motivation in the animal (or human) and instigate approach responses in relation to themselves through the 'impulsive system'. However, internal factors associated with deprivation states (such as withdrawal) are viewed as a 'gate' that determines how effective the incentive input is in exciting the motivational circuits that 'pull' and 'steer' the animal (or human) toward the appropriate goal object. This process, we propose, is dependent on the insula. Feedback loops arising from the body, reflecting the status of the viscera and homeostasis, and mediated through the insula, will adjust the strengths of the conflicting signals, thereby sensitizing the impulsive system, and potentially over-riding the inhibitory control of the reflective system. An additional possibility is that insula signals may subvert the decision-making processes of the reflective system into formulating plans for action to seek and procure drugs.

agency in healthy participants [66] and in addicts [26••]. Anatomically, the insula is a primary site for receiving interoceptive signals, but in turn the insula is connected to widespread regions of the prefrontal cortex, and hence this interoceptive-prefrontal interaction may be mediated by the insula [26••,67].

Conclusion and future directions

The discovery of the important role of the insula in specifically smoking addiction does not undermine the seminal work generated to date on the roles of other components of the neural circuitry implicated in addiction, and impulse control disorders in general, especially the mesolimbic dopamine system (incentive habit system), and the prefrontal cortex (executive control system). Addressing the role of the insula only complements this prior work, and advances our efforts for finding novel therapeutic approaches for treating several impulse control disorders, including breaking the cycle of addiction. The most obvious is that therapeutically modulating the

function of the insula, may make it easier to overcome one's addiction and other impulse control problems [48••,68]. This could be accomplished by designing new pharmacological therapies that target receptors within the insula, invasive techniques such as deep brain stimulation, or non-invasive techniques such as repetitive transcranial magnetic stimulation [69,70•]. Another but compatible option is by implementing therapies aimed to improve awareness of the body, such as biofeedback training or body-focused meditation [48••]. This might be particularly efficient in those addicted persons with little bodily reactivity or poor perception of this signal (poor insight) [56] and who rely on non-emotional sources to run decision-making processes [48••], possibly because of a dysfunctional neural mechanism that includes the insula and medial prefrontal cortex [71]. Cognitive reappraisal techniques focusing on adequate interpretation of emotional input may be beneficial for those of addicts for whom low signal and poor perception rely on a rewarding representation of ideal body states, a process that hypothetically operates through insula/striatal/amygdala network [68].

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