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Brain Struct Funct. Author manuscript; available in PMC 2013 July 02.

Published in final edited form as:
Brain Struct Funct. 2010 June ; 214(0): 435–450. doi:10.1007/s00429-010-0268-7.

The insula and drug addiction: an interoceptive view of pleasure, urges, and decision-making

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Abstract

We have recently shown that damage to the insula leads to a profound disruption of addiction to cigarette smoking (Naqvi et al., Science 315:531–534, 2007). Yet, there is little understanding of why the insula should play such an important role in an addictive behavior. A broad literature (much of it reviewed in this issue) has addressed the role of the insula in processes related to conscious interoception, emotional experience, and decision- making. Here, we review evidence for the role of the insula in drug addiction, and propose a novel theoretical framework for addiction in which the insula represents the interoceptive effects of drug taking, making this information available to conscious awareness, memory and executive functions. A central theme of this framework is that a primary goal for the addicted individual is to obtain the effects of the drug use ritual upon the body, and representations of this goal in interoceptive terms by the insula contribute to how addicted individuals feel, remember, and decide about taking drugs. This makes drug addiction like naturally motivated behaviors, such as eating and sex, for which an embodied ritual is the primary goal.

Keywords

Insula; Drug addiction; Emotion; Reward; Interoception; Learning; Motivation; Lesion effects; Neuropsychology

Overview of the neurobiology of drug addiction

Drug addiction is a cause of tremendous emotional, financial, medical, and legal costs to individuals and society. For example, cigarette smoking is the single largest preventable risk factor for morbidity and mortality in the developed world (Peto et al. 1992); nearly half of all of state prison inmates were under the influence of alcohol or drugs at the time of their offense (Spiess and Fallow 2000); drug overdose is the second leading cause of unintentional death in the US (Paulozzi 2008); and more than 40% of all traffic accidents in the US are attributable to alcohol (Stinson and DeBakey 1992). Drug addiction is rooted in long-term adaptations within the brain that promote escalating drug use, difficulty quitting,

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and relapse—all despite awareness of negative consequences. Understanding the neural substrates of addiction is an important step in the development of effective treatments.

Traditional animal models of the neurobiology of drug addiction have focused largely on the role of the dopamine system in driving compulsive drug self-administration. These models have converged on the idea that all drugs of abuse are addictive because taking these drugs is rewarding, and that this reward is mediated by facilitation of dopamine release from ventral tegmental area neurons that project to the nucleus accumbens and amygdala (Wise and Bozarth 1987; Koob et al. 2004; Berke and Hyman 2000). While animal models of drug self-administration possess a high level of face validity in that they capture the essential behavioral feature of addiction, they fail to integrate several facets of human drug addiction that may be important for treatment. For example, they do not explain why the attractiveness of drug use increases in the face of tolerance that significantly reduces a drug's pleasurable, i.e. rewarding, effects. Furthermore, most animal models do not take into account the deep ambivalence that most human drug users have about their drug use. Finally, animal models rely upon the observation of external behavior and cannot address internal, subjective experience; in an addicted individual who remains abstinent despite strong urges, subjective experience may diverge in important ways from externally observable behavior.

In their incentive-sensitization model of addiction, Robinson and Berridge (2001) have addressed some of the limitations of traditional animal models by proposing a distinction between the pleasure obtained from taking a drug (liking), and the incentive motivation underlying drug seeking behaviors that increase the likelihood of consuming a drug (wanting). They propose that addiction results from long-term biochemical, physiological and structural adaptations within neural systems for wanting, which sensitize them to the effects of drugs and drugassociated stimuli. These systems include the mesolimbic dopamine system and its projections to the amygdala and nucleus accumbens. At the same time, they propose, drugs of abuse do not sensitize neural systems for drug liking (their model does not specify what the systems for drug liking are, though it does describe neural systems that mediate liking for natural rewards—these include the parabrachial nucleus and the ventral pallidum). This distinction between liking and wanting explains, for example, why drug seeking can increase in the face of decreasing subjective pleasure from drug taking because of tolerance.

A further refinement made by Robinson and Berridge (2001) and Berridge and Robinson (2003) is the distinction between two forms of drug wanting. One form is conscious, goal-directed, and depends upon knowledge of the relationship between specific actions and the value of their outcomes. This explicit form of wanting is manifested in conscious feelings of urge to take a drug, as well as in decision-making processes that involve recall of past outcomes of drug use. The other form of drug wanting is largely non-conscious, habitual, and does not require knowledge about the relationship between drug taking and its outcomes. This implicit form of wanting explains, for example, how relapse can occur in the absence of conscious urges to use drugs, as well as how drug seeking can escalate in the face of decreasing pleasure from drug taking because of tolerance. Implicit wanting is seen, for example, in laboratory phenomena such as cue-elicited relapse and Pavlovian to instrumental transfer, where devaluation of outcomes does not reduce the strength of instrumental responding. Robinson and Berridge have proposed that implicit wanting is mediated by the dopamine system and its subcortical projections to the amygdala and nucleus accumbens, whereas explicit wanting is mediated by cortical regions, including the orbitofrontal/ventromedial prefrontal cortex (OFC/VMPFC) (Wang et al. 1999). Everitt and Robbins (2005) have made a similar distinction between voluntary drug seeking that is driven by expectations of the positive hedonic effects of drug taking, and compulsive drug seeking that is independent of knowledge about the outcomes of drug taking. However, in

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their model, drug addiction represents a shift from voluntary drug seeking, mediated by the OFC/VMPFC and the nucleus accumbens, to involuntary drug seeking compulsions, mediated by the dorsal striatum, with dopamine playing a role in this transition.

Human neuroscience models of drug addiction have focused largely on the neural activity elicited by passive exposure to drugs and drug-related stimuli. Numerous functional imaging studies have revealed that exposure to environmental cues associated with drug taking activates a network of largely cortical areas (Table 1). A consistent finding from these studies is that subjective urges elicited by drug cue exposure are correlated with activity in the OFC/VMPFC, anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC) and insula, suggesting that these cortical regions function together in generating the subjective experience of urge. This pattern of activity is consistent across a variety of drugs of abuse, including psychostimulants, alcohol, opiates, and tobacco [see the review of functional imaging studies of cue-induced urge in this issue by Garavan 2010]. A limitation of functional imaging studies is that while they show that activity within a given region is correlated with subjective urges, they do not demonstrate that the region is critically necessary for this experience. Furthermore, it is a matter of debate whether conscious urges are actually an important factor in promoting drug addiction (Tiffany 1990).

Recent work in human substance abusers has focused on the role of executive functions in drug addiction, specifically, how dysfunction in cortical networks for decision-making and cognitive control contributes to maladaptive patterns of drug use in the face of negative consequences. We have previously hypothesized that addiction is caused in part by an imbalance between an “impulsive” system that governs appetitive motivation and is driven by immediate rewards on the one hand and a “reflective” system that regulates and controls the impulsive system according to future pleasurable or aversive consequences (Bechara 2005). According to this model, the impulsive system includes the dopamine system and its targets in the amygdala and striatum, including the nucleus accumbens. The reflective system includes prefrontal areas, such as the DLPFC, the OFC/VMPFC and the ACC. This view posits that chronic exposure to drugs of abuse leads to neural plasticity that sensitizes the impulsive system to drugs and drug related stimuli, and also leads to hypo-functioning of the reflective system that renders it less capable of regulating the impulsive system. The insula was initially hypothesized to be part of the reflective system within this framework, as an important component in decision-making processes that control drug use. This idea was supported by a study by Paulus et al. (2005), showing that a lower level of activity in the insula during a simple decision-making task predicts relapse to amphetamine use, suggesting that hypofunctioning of the insula contributes to relapse. We have now revised the role of the insula in this model, as explained in more detail later, to suggest that functional engagement of the insula in response to drug-related signals exacerbates the imbalance between the impulsive and reflective systems, intensifying activity of the impulsive system and further disabling the regulatory function of the impulsive system.

The insula is a critical neural substrate for addiction

Among the numerous brain regions implicated in addiction, we became interested in the insula for a number of reasons. First, though a large number of functional imaging studies have demonstrated that activity in this region is correlated with conscious urges to use drugs, the role of conscious urges in driving addiction has been a matter of debate (Tiffany 1990). Therefore, it is important to understand whether a region that may be critically necessary for conscious urges is actually important for addiction. Second, the insula may play an important role in decision-making processes that help drug addicted individuals control their use, i.e. the reflective system. Which of these two hypothesized roles for the insula—a driver of conscious drug urges versus a regulator of drug use—predominates is not clear.

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To address the role of the insula in addiction, we performed a study examining the effects of insula damage in human cigarette smokers (Naqvi et al. 2007). We chose the lesion approach because it allows for a determination of whether a brain region is critically necessary for a psychological process, even one as complex as addiction. In this study, we hypothesized that damage to the insula would result in an increased likelihood of disruption of addiction to smoking, compared to damage in other regions of the brain. We included subjects who were regular smokers at the time that they sustained damage that included either the right or left insula. We also included matched comparison subjects who were smokers at the time they sustained damage to non-insular regions. First, we compared the rate of quitting smoking among these groups, and found that smokers with insula damage were more likely than smokers with non-insula damage to quit smoking after the onset of their brain damage (68% of subjects with insula lesions quit, compared to 38% of subjects with non-insula lesions), but that this difference was not statistically significant. This lack of statistically significant difference was not surprising, since smokers who suffer a brain injury of any kind are likely to quit smoking.

The real question, then, was how insula damage affected the ease of quitting. To examine this, we retrospectively assessed the experience of quitting smoking in all of the subjects who quit smoking after their brain injury. We classified subjects as having undergone a "disruption of addiction" to cigarette smoking if they met all of the following criteria: (1) they quit smoking immediately after their brain injury; (2) they never smoked again after their brain injury; (3) they rated the difficulty of quitting as less than 3 on a 1–7 scale; and (4) they never felt an urge to smoke again after their brain injury. We found that smokers who sustained insula damage (either left or right side) were significantly more likely to undergo a "disruption of addiction" than smokers who sustained non-insula damage (12/19 subjects with insula damage vs. 4/50 subjects with non-insula damage; adjusted odds ratio = 22.5; $P = 0.0005$). When examining each side separately, we found effects of lesions in both the right insula (adjusted odds ratio = 10.87, $P = 0.0003$) and left insula (adjusted odds ratio = 3.61; $P = 0.001$). A higher proportion of subjects with right insula damage underwent a disruption of cigarette smoking addiction (5/6 subjects), compared to subjects with left insula damage (7/13 subjects), however, the laterality effects could not be verified statistically due to a small sample size. Importantly, subjects with insula damage who underwent a disruption of addiction did not report any changes in their appetite or pleasure from eating, suggesting that the effects of insula damage were relatively specific to smoking addiction, as opposed to general motivational effects.

The results of this study provide direct evidence that the insula is critical for psychological processes that maintain addiction to cigarette smoking, namely conscious urges to smoke. The study is limited by its relatively small size, and by the use of a retrospective evaluation of the experience of quitting (Vorel et al. 2007). In addition, it has been shown that insula lesions in humans are associated with "anergia," or a subjective sense of tiredness; such an effect could contribute to a disruption of addiction in a non-specific way (the more general cognitive and behavioral effects of insula lesions in humans are reviewed in this issue by Ibanez et al. (2010)). These limitations are currently being addressed by a prospective study examining a larger cohort of patients. In addition, the study did not address several important questions about the role of the insula in addiction. For example, are the effects of insula damage specific to tobacco addiction, or could they be generalized to other drug addictions? In addition, what are the specific psychological processes that the insula contributes to conscious urges, and how are these different from processes contributed by other regions that have been implicated in conscious urges, e.g. the OFC/VMPFC, ACC, and DLPFC? (In this study, damage to these regions was not found to be significantly associated with a disruption of addiction).

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A subsequent study by Contreras et al. (2007) addressed some of these limitations by examining the effects of reversible insula inactivation on methamphetamine place preference in rats. In this study, rats were given a choice between entering either a white compartment or a black compartment. They initially preferred to enter the black compartment, presumably due to an innate preference that evolved to reduce the risk of detection by predators. During training, each time the rats entered the white compartment they received an injection of methamphetamine. After training, the rats tended to prefer entering the white compartment, demonstrating the learning of an association between entering the white compartment and methamphetamine delivery. Injection of lidocaine, a reversible inhibitor of neuronal activity, into the insula bilaterally resulted in the rats reverting to a preference for the black compartment. Over time, as the lidocaine wore off, the rats began to prefer the white compartment again, demonstrating reversibility of the disruption in conditioned place preference.

The findings of Contreras et al. extend our work on the effects of insula lesions in human smokers to a different drug of abuse and to an animal model. They also address the specific behavioral processes that the insula may contribute to addiction, namely, the learned association between environmental cues and drug effects. Conditioned place preference bears some resemblance to the classical conditioning process thought to underlie cue-induced urges, where environmental cues (conditioned stimuli) that are repeatedly paired with drug use (unconditioned stimuli), come to elicit conditioned responses (e.g. drug wanting, autonomic responses), that are related in some way to the physiological responses elicited by drug use (unconditioned responses) (O'Brien et al. 1998; Tiffany 1999). The results suggest that the insula is involved either in the storage or in retrieval of information about the association between environmental cues and drug effects, though they do not distinguish between these two. Interestingly, the conditioned place preference paradigm used in this study required that the animals choose between the safety of the black compartment and receiving the drug in the white compartment at some perceived risk. This process involves explicit knowledge of action-outcome contingencies, similar to the conscious, goal-directed wanting conceptualized by Robinson, Berridge, Everitt and Robbins (Robinson and Berridge 2001; Berridge and Robinson 2003; Everitt and Robbins 2005). It also resembles decision-making processes that we have proposed to be disrupted in drug addiction, such that addicted individuals choose to take drugs despite awareness of potential negative consequences (Bechara 2005).

The role of the insula in integrating interoception into emotions and decision-making

Our results from cigarette smokers with insula damage, along with functional imaging studies of cue-induced drug urges and reversible inactivation studies in rats, suggest that the insula is a critical neural substrate for conscious urges, and that conscious urges are an important factor in promoting ongoing drug use. Conscious cue-induced urges are a kind of emotion, in that they are states of the organism, elicited by external objects that possess value, that are associated with conscious feelings, bodily responses (e.g. autonomic arousal) and motivated behaviors.

Damasio (2000) was the first to propose that the insula is a critical neural substrate in conscious emotional experience, or feeling. Specifically, he hypothesized that emotional feelings arise when the physiological state is perturbed by an emotional stimulus, which can include autonomic responses elicited by an external object, as well as changes in the internal state triggered by direct physical contact with an object, such as taste, gastric distention, and tissue damage. He further hypothesized that brain regions that "map" the body, such as the insula, represent the bodily changes elicited by emotional stimuli, and that this mapping

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gives rise to conscious feeling. This is essentially a neurobiological formulation of the James–Lange theory of emotion (James 1884). Craig (2002) refined this model, detailing the anatomical and physiological evidence for the role of the insula in body state representation and emotional feeling. According to Craig, the insula functions to map the ongoing physiological state of the body, including the gut, the cardiovascular system, the airway and the solid viscera, as well as a variety of physiological processes within the muscle, bone, integument and immune system. These physiological processes are special in that they play a direct role in survival and the maintenance of homeostasis. Craig has termed this process of mapping the internal state of the organism interoception. Information about these physiological changes reaches the insula through a thalamocortical pathway that is dedicated to interoception. This information is passed anteriorly and ventrally within the insula, from granular insula to agranular insula. Conscious interoception occurs when these physiological changes are mapped within the anterior insula, in particular the right anterior insula. (The anatomical, physiological, and behavioral evidence for the role of the anterior insula in conscious interoception, and for the lateralization of this process, is reviewed in this issue by Craig (2010)).

Conscious interoception, however, is not the same as an emotional feeling (Bechara and Naqvi 2004). According to Damasio (2000), conscious emotional feelings occur only after representations of the physiological changes and representations of the emotional objects that elicit them are integrated within areas that receive projections from both exteroceptive cortex (e.g. higher-order visual and auditory cortices) and the insula. Damasio has proposed that this integration occurs in areas such as the ACC (see the reviews in this issue by Medford and Critchley (2010), as well as by Allman et al. 2010, on the functional relationships between the insula and the ACC). Damasio has also posited that the insula plays a role in an “as–if” representation of the bodily state, in which exposure to an emotional object that has activated a bodily state in the past can activate a representation of that bodily state within the insula, even when there is no change in the body itself (Damasio 1994). This can be considered a form of interoceptive memory, as well as a form of mental time travel, where the insula instantiates a representation of the internal state of the organism at some future or past time. Such a role is supported by a Lovero et al. (2009), showing that the intensity of insula activity elicited by cues that have been previously paired with a bodily stimulus is related to the intensity of the bodily stimulus, suggesting that the cue activates a sensory representation of the bodily stimulus that has been encoded into memory. According to Craig (2009), such processes allow the insula to participate in the comparison of different feelings to each other.

The insula has been shown in a large number of functional imaging studies to be activated by a variety of primary emotions, including fear, sadness, anger and disgust (see the meta-analysis by Phan et al. 2002). Furthermore, lesions of the insula have been associated with asymbolia for pain (Berthier et al. 1988), depressive symptoms (Manes et al. 1999) and an impaired experience of disgust (Calder et al. 2000), suggesting an important role in conscious emotional feeling (the effects of insula lesions in humans are reviewed in this issue by Ibanez et al. (2010)). In addition, the insula is frequently activated during fear conditioning (see the meta-analysis by Sehlmeyer et al. (2009).). Interestingly, insula activation during fear conditioning appears to depend upon both awareness of the feared stimulus as well as the level of input from the viscera (Critchley et al. 2002). This supports the notion that the insula’s role in emotional learning is tied to the linking of interoception to conscious awareness, as proposed by Craig (2009).

The insula is involved in signaling of bodily states elicited by the consumption of natural rewards. The insula has been identified as the primary taste cortex (Rolls and Rolls 2005). Functional imaging studies in humans have shown that the insula is activated by the taste of

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palatable foods (reviewed in this issue by Small 2010), along with the sensation of water in the mouth (de Araujo et al. 2003), gastric distention (Wang et al. 2008), genital stimulation (Georgiadis et al. 2005) and sensual touch (Olausson et al. 2002). It appears that the insula represents stimulus properties, such as the intensity or identity of a taste, as opposed to its hedonic value, which appears to be processed in downstream regions, such as the amygala and the orbifrontal cortex (Yaxley et al. 1988; Rolls et al. 1989). The insula is also activated by appetitive feelings such as hunger (Del Parigi et al. 2002; Pelchat et al. 2004; Wang et al. 2004), thirst (Egan et al. 2003; Farrell et al. 2006), and sexual desire (Arnow et al. 2002; Karama et al. 2002; Stoleru et al. 1999), which are all states of conscious wanting that have as their primary object an embodied consummatory ritual. One hypothesis, yet untested, is that insula activity during such appetitive feelings is related to an interoceptive memory of the consummatory ritual.

The insula also plays a role in executive functions. In his somatic marker model for decision-making, Damasio (1994) first hypothesized that the insula plays a role in decision-making in which outcomes, either rewarding or punishing, are uncertain. He proposed that such decisions depend upon bodily states that mark potential outcomes as being either rewarding or punishing. According to Damasio, these bodily states are triggered by areas, such as the amygdala and the OFC/VMPFC, that integrate information about the external world with information about goals and the internal state of the organism, and send outputs to the body via effector regions in the brainstem and hypothalamus. These bodily states then feed back to the brain and are mapped in areas that represent the body, including the insula. This model overlaps to a significant degree with Damasio's model for conscious emotional feeling, and includes a role for "as–if" representations of bodily states in regions such as the insula. This process biases decisionmaking towards the outcome that maximizes reward and minimizes punishment. The role of the insula in decisionmaking under uncertainty and risk has been substantiated by a number of functional imaging and human lesion studies (reviewed in this issue by Bossaerts et al. 2010). The emerging view from these studies is that the insula functions in the computation of the level of risk associated with specific actions. It remains to be seen whether the processing of bodily states by the insula is necessary for this computation.

Animal work on the role of the insula in decisionmaking has focused largely on studies of goal-directed behavior in rodents. Goal-directed behaviors take into account knowledge about the relationship between specific actions and their specific outcomes, as well as knowledge about the current hedonic value of these outcomes. Goaldirected behaviors are distinguished from simple Pavlovian instrumental learning and habits, which persist in the face of devaluation of outcomes, e.g. by satiety (this is as analogous to the distinction between conscious wanting and non-conscious wanting). Dickinson and Balleine (2000) have shown that lesions of the insula in rodents alter goal-directed behavior by disrupting the ability to encode the sensory impact of specific rewarding outcomes into memory, impairing the ability retrieve knowledge about the hedonic value of these outcomes. In this same study, they showed that insula lesions do not disrupt simple Pavolovian instrumental learning.

A sizeable literature has also examined the role of the insula in conditioned taste aversion, where an animal is taught to associate a novel taste with an aversive visceral stimulus (e.g. lithium chloride injection), and subsequently avoids that taste. It has been shown that lesions of the insula disrupt the acquisition and expression of conditioned taste aversion (Cubero et al. 1999). Acquisition of conditioned taste aversion is associated with increased tyrosine phosphorylation in the insula (Rosenblum et al. 1995) and depends upon protein synthesis in this region (Rosenblum et al. 1993). Conditioned taste aversion has been shown to depend upon dopaminergic innervation of the insula (Zito et al. 1988), which expresses a high

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concentration of D1 dopamine receptors (Hurd et al. 2001). It remains to be seen whether dopamine signaling in the insula is necessary for learning about rewarding stimuli. However, given the effects of drugs of abuse on the dopamine system, it is tempting to speculate that dopamine-dependent learning processes within the insula play a role in addiction.

The role of interoception in addiction

Given the importance if the insula in both drug addiction and interoception, the question arises as to the role of interoception in addiction. A longstanding assumption of neurobiological models of addiction has been that the primary goal of drug use is to obtain the rewarding effects that result from the drug binding at receptors in the brain, i.e. the facilitation of dopamine release from VTA neurons. In addition to their direct CNS effects, nearly all drugs of abuse exert powerful effects on the periphery: visceral effects on the cardiovascular system, the airway, and the gut; taste sensations and pain sensations arising from the integument and pharynx. For example, it is widely known that cocaine, amphetamine, marijuana, and nicotine are all potent stimulators of the autonomic nervous system, eliciting increases in heart rate and blood pressure, along with peripheral vasoconstriction. Aversive effects of opiates, such as nausea and constipation, are mediated by peripheral receptors (Bechara and van der Kooy 1985). Intravenous and subcutaneous injections of various drugs are painful because they involve violation of the body envelope. Alcohol has a strong taste, as well as chemosensory effects in the pharynx. Cigarette smoking, in addition to its autonomic effects, has highly salient sensory effects within the airway, as well as a strong taste.

Bodily effects play an important role in the subjective feeling of taking a drug. This phenomenon has been extensively studied for cigarette smoking. For example, it has been shown that the airway sensory effects of smoking are effective at eliciting feelings of pleasure (Westman et al. 1996; Naqvi and Bechara 2005), reducing urges (Westman et al. 1996, 1995) and promoting abstinence (Westman et al. 1995; Levin et al. 1993). Moreover, it appears that airway stimulation may be more rewarding to addicted smokers than the direct CNS effects of nicotine (Westman et al. 1996). This may be why nicotine replacement, the current first-line treatment for smoking addiction, is only modestly effective at preventing relapse (Etter and Stapleton 2006); it may be that the primary goal that is pursued by smokers is the effect of smoking upon the body, and that addicted smokers continue to desire this goal during nicotine replacement.

It may seem farfetched to think that the peripheral effects of drug use play an important role in drug motivation and reward, but this makes sense if one considers the evolutionary function of brain systems that govern motivation and reward. All natural rewards, such as food, sex, hydration, and sensual touch, stimulate the body in characteristic ways. For example, taste, along with gastric distention, signals attainment of nutrition; the sensation of fluid in the mouth signals the attainment of hydration; stimulation of the genitals signals copulation; sensual touch signals the attainment of affiliative contact and nurturing. What ties all of these consummatory behaviors together is that they are important for survival and the maintenance of homeostasis, i.e. without performing these behaviors, the organism would fail to pass on its genes. They each possess positive hedonic value that is derived from their sensory effects, i.e. without their peripheral effects, these behaviors would not be very pleasurable [this is related to Craig's concept of "homeostatic emotion" (Craig 2009)]. Importantly, all of these sensations are signaled in the insula.

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A model for the role of the insula in drug addiction

We propose that the insula plays a role in three related processes that are important for drug addiction: (1) the conscious pleasure that is derived from the interoceptive effects of drug taking; (2) the recall of the pleasurable interoceptive effects of drug taking during conscious cueinduced urges; and (3) decision-making processes that involve weighing the pleasurable interoceptive effects of drug taking against the negative consequences of drug use, which may have their own interoceptive effects. What ties all of these processes together is the representation of the interoceptive effects of drug taking by the insula in a form that is explicit, i.e. available to conscious awareness, working memory and long-term declarative memory.

Conscious pleasure

Drug taking rituals exert characteristic effects on the body that are transmitted to the brain via specific interoceptive pathways. We propose that these bodily (peripheral/visceral/interoceptive) states are an important component of the conscious sensory experience of pleasure that is specific for each drug use ritual. In other words, snorting cocaine feels different from drinking alcohol because each of these behaviors elicits a distinct bodily state, even though they both cause release of dopamine. The bodily effects of drug taking act as a signal for attainment of the drug, similar to the way in which taste is a signal for the attainment of nutrition, or genital stimulation is a signal for copulation. The bodily states elicited by drug taking are represented within the insula, giving rise to specific feelings that are associated with taking that drug. We propose that pleasure— which is an hedonic emotional experience, as opposed to mere conscious sensory perception—occurs when the insula representation of the bodily effects of drug use is relayed to downstream areas, such as the amygdala and OFC/VMPFC. These regions integrate the sensory information about drug use from the insula with information about homeostatic and goal-related processes that may modulate pleasure, such as drug withdrawal and expectancy, and also receive dopaminergic projections from the VTA, which may modulate the hedonic impact derived from interoceptive effects of drug taking (Fig. 1). In terms of which contributes more to the conscious experience of pleasure—interoceptive effects or direct CNS effects—we believe that both are necessary for the full experience of pleasure from drug taking. In the case of drugs for which direct CNS effects by themselves provide relatively little primary reinforcement, e.g. nicotine (Dar and Frenk 2002, 2004), peripheral effects may play a larger role in drug taking pleasure. Thus, we hypothesize that damage to the insula disrupts conscious awareness of the interoceptive effects of drug use, which leads to diminished pleasure during drug taking.

From preliminary results of an ongoing study (Naqvi 2006), we found that subjects who did not quit smoking after left insula damage showed a reduction in the ability to perceptually and to hedonically discriminate between puffs of cigarettes that provided different levels of airway sensory stimulation. In a previous study in neurologically intact smokers (Naqvi and Bechara 2005), we found that individual puffs from cigarettes that contain nicotine (which deliver a higher sensory impact) are experienced as stronger, more pleasurable and more desirable than individual puffs from cigarettes that do not contain nicotine. In that study, subjective responses were obtained within 5 s of inhalation of the puffs (before nicotine reached the CNS), which meant that differences in the hedonic impact of the puffs could not be attributed to the direct CNS effects of nicotine. We used the same paradigm in smokers with left insula lesions ($N = 5$), comparing them to smokers with damage in regions that did not include the insula ($N = 5$). (We only included subjects with left insula damage because nearly all subjects with right insula damage in our sample stopped smoking after their brain injury.) We found that whereas lesioned comparison subjects found nicotinized puffs to be stronger, more pleasurable and more desirable than denicotinized puffs, subjects with left

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insula lesions found the nicotinized and denicotinized puffs to be equally strong, pleasurable and desirable (Fig. 2). This provides preliminary evidence that the left insula is necessary for the ability to consciously appreciate and derive pleasure from the bodily impact of smoking.

Conscious cue-induced urges

We propose that exposure to drug-associated cues within the environment, such as the sight of another person using drugs, activates a representation of the interoceptive effects of the drug use ritual within the insula. This gives rise to a conscious experience of urge that recalls the specific interoceptive effects of drug use. Through this process, conscious cue-induced urges come to be "about" specific drug use rituals, as opposed to general motivational states that have no specific goal. Thus, the urge to smoke crack feels different from the urge to smoke cigarettes, even in an individual who is addicted to both drugs. Conscious cueinduced urges are tied to memories for the bodily effects of the drug use ritual, instantiated within the insula. This may be why one of our patients who suffered insula damage reported that "my body forgot the urge to smoke" (Naqvi et al. 2007). Interestingly, this same patient reported that, in his dreams, smoking lost much of its pleasurable qualities and had even become an aversive experience.

We propose that cue-induced urges are triggered by areas, such as the amygdala and the OFC/VMPFC, that receive information about the presence of drug-related cues in the external environment, and integrate this with information about goals and expectations (e.g. the availability of the drug) and the internal state of the organism (e.g. the level of drug withdrawal). The OFC/VMPFC in particular is interconnected with other prefrontal cortical areas, such as the DLPFC (Morecraft et al. 1992), that are involved in maintaining representations of emotional objects "in mind" when the objects are attended to, or when they are recalled from long-term memory. The amygdala (Allen et al. 1991) and OFC/VMPFC (Hurley et al. 1991) send projections to the insula. We propose that these projections function to activate an "as–if" representation of the interoceptive effects of drug taking. The amygdala and OFC also send outputs to bodily effector regions in the brainstem and hypothalamus that trigger autonomic and other bodily responses to drug cues (Naqvi 2006; Krettek and Price 1978). These bodily responses also feed back to the insula, contributing to the conscious feeling of urge. The body state representation that is thus engendered gives rise to conscious feelings of urge through the insula's connections with areas that integrate representations of the body with representations of the external world. Such areas may include the ACC, as has been proposed by Damasio (2000). Through its connections with the ventral striatum (Chikama et al. 1997), the insula also acts as a "gate" through which memories for the interoceptive effects of drug taking motivate drug-seeking behaviors. This gate may be particularly permissive and difficult to close because of long-term plasticity at connections between the insula and ventral striatum (Fig. 3).

This form of cue-induced urge is related to the conscious wanting postulated by Robinson and Berridge (2001), in that the organism is conscious of the feeling or urge, and that the urge is goal-directed, i.e. it is about a specific object. It is distinct from non-conscious/implicit wanting and drug use "habits", which are not goal-directed and which are mediated primarily by the dopamine system and its projections to the dorsal striatum (Everitt and Robbins 2005). Thus, damage to the insula is hypothesized to disrupt conscious wanting/cue-induced urge, but to spare non-conscious/implicit wanting. This may be why some patients with insula damage continue to smoke after their brain injury; they continue to have the implicit motivation to smoke, even though they may not feel a conscious urge to do so.

In an unpublished study (Naqvi 2006), we examined conscious cue-induced urges among subjects with insula damage who did not quit smoking after their brain injury. These were, again, all subjects with left insula damage ($N = 5$). We exposed these subjects to another

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person smoking, as well as to a control stimulus (the same person drinking water). We performed the same procedure in lesioned comparison subjects who were smokers with damage in regions that did not include the insula ($N = 5$). We found that both insula lesioned and comparison subjects both had increases in conscious urges after being exposed to the smoking cue, compared to the control stimulus, though the difference between the cue and the control stimulus was not significant in insula lesions subjects (Fig. 4a). Furthermore, neither group showed a decrease in the severity of smoking dependence after their brain injury (Fig. 4b). This finding is preliminary, given the small sample size, but it suggests that subjects who continue to smoke after left insula lesions continue to experience cue-induced urges. It may be that some other region (e.g. the right insula) continues to support conscious urges after left insula damage in these subjects.

A note on drug withdrawal

Cue-induced urges, which are caused by exposure to drugrelated information in the environment, are to be distinguished from withdrawal urges, which are caused by discontinuation of the drug. Withdrawal urges reflect the unmasking of homeostatic adaptations in multiple brain and body systems to chronic exposure to the drug (these are related to the adaptations underlying tolerance). There are a number of important differences between withdrawal urges and cue-induced urges: whereas cue-induced urges are long-lasting, i.e. they can be triggered after years of abstinence, withdrawal urges typically last days to weeks; while withdrawal urges can be reversed by replacing the drug (usually in a longer-acting form), cue-induced urges usually persist after drug replacement (Tiffany et al. 2000); while cue-induced urges are more likely to play a role in relapse after a sustained period of abstinence, withdrawal urges likely predominate in the early (i.e. detoxification) stages of abstinence.

Early theories of drug addiction (Wikler 1948) have posited that withdrawal urges are a negative hedonic state, and that the motivation to take drugs is rooted, in part, in a motivation to alleviate this negative hedonic state, i.e. negative reinforcement. More recent models (Koob and Le Moal 2001) have posited that chronic drug use leads to a change in reward set-point, such the individual requires increasing quantities of the drug in order to achieve the same effects, and also obtains less reward from more adaptive reinforcers, a process termed allostasis. This is process occurs through plasticity within the mesolimbic dopamine system, as well as through alterations in the stress responses system. According to this view, drug discontinuation leads to elevation of stress response and a decreased in brain reward functioning. Drug-seeking motivation induced by drug discontinuation, then, occurs as a means to return the individual to the allostatic setpoint.

The bodily effects of drug use play an important role in drug withdrawal. Chronic use of many drugs of abuse leads to adaptations within the autonomic nervous system and its target organs that become unmasked when drug use is discontinued. This is well known to anyone who has treated withdrawal from alcohol, opiates, and nicotine. It may be that these derangements contribute to the experience of withdrawal urges. This may be why, for example, medications that modulate the autonomic nervous system, such as clonidine and propranolol are effective at reducing withdrawal urges for opioids (Gowing 2004) and cocaine (Kampman et al. 2001), respectively.

We hypothesize that the insula plays a role in the motivational state elicited by drug discontinuation, i.e. drug withdrawal. We hypothesize that withdrawal-associated bodily changes are mapped within the insula. In addition, elevated stress response can be signaled within the insula via corticotropin releasing factor receptors, which are richly expressed within the insula (Sanchez et al. 1999). These receptors may play a role in signaling the stress response to drug withdrawal, which may interact with interoceptive signals arising

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from the viscera during withdrawal to give rise to an overall bodily state representation of drug withdrawal. This representation can reach motivational and emotional systems in the ventral striatum, amygdala and OFC/VMPFC and exert a number of influences. This may include magnifying the positive incentive properties of drug-associated stimuli (i.e. cue-induced urges), as well as enhancing the aversive properties of negatively valenced affective and social stimuli (i.e. irritability). In parallel, the bodily state of withdrawal gives rise to a conscious feeling of withdrawal urge.

We have begun to collect data on withdrawal symptoms in patients with insula lesions. Our preliminary results show that these patients experience symptoms of nicotine withdrawal (anxiety, insomnia, depression, difficulty concentrating, impatience, irritability/anger and restlessness), even though they did not experience urges to smoke after their brain damage. This may be because insula lesions by themselves can cause symptoms that resemble nicotine withdrawal, even in patients who have never smoked. Another possibility, consistent with our proposed model, is that patients with insula damage are able to experience withdrawal symptoms, but are impaired in their ability to link these symptoms with the goal of smoking. Further study is required to distinguish between these two possibilities.

Decisions to quit and relapse

Much of the day-to-day drug use in an addicted individual occurs without a great deal of thought—without conscious urges or without any particular conflict about drug use. Under these circumstances, drug use is likely driven by largely automatic processes, such as implicit wanting (Tiffany 1990). In contrast, the process of quitting drug use and the process of relapsing when there is an awareness of negative consequences are both complex decision-making processes that involve weighing the positive hedonic effects of drug use against negative social, emotional, medical, financial, and legal consequences.

As discussed above, the insula has been shown to play a role in decision-making processes that involve weighing uncertain positive and negative consequences. We propose that the insula is involved in weighing the positive and negative consequences of drug use when individuals decide to quit using drugs and when they attempt to avoid relapse. In these situations, the individual recalls both the positive hedonic consequences of drug taking as well as the negative hedonic consequences of drug taking. We propose that the positive hedonic consequences of drug taking are encoded in the insula in terms of the bodily effects of the drug taking ritual. The recall of these positive hedonic consequences occurs much in the way that it does when an individual recalls prior drug experiences and experiences conscious urges—through the coordinated action of the insula with the amygdala, OFC/VMPFC and the DLPFC. This recall may also be experienced as an urge to use the drug. At the same time, this system also functions in the recall of the negative consequences of drug use in interoceptive terms, i.e. in terms of how the negative consequences will affect the integrity of the body, survival and the maintenance of homeostasis. These representations are concurrently activated within the insula. The ACC functions within this model to signal conflict between the goal of drug taking and the competing goals, which is necessary to shift attention from the drug use goal to the competing goal. The insula connection to the ventral striatum functions to bias behavior towards drug seeking vs. the alternative goal (Fig. 5).

We propose that decision to abstain depends upon the ability to suppress the representation of the positive hedonic effects of drug use and to enhance the representation of the negative consequences of drug use. We further propose that relapse occurs when the representation of the positive hedonic effects of drug taking “win out” over representations of the negative consequences of drug taking. This occurs because the representation of the positive hedonic effects of drug taking is much stronger than the representation of the negative consequences

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of drug taking. This leads to an allocation of attention toward drug-seeking goals, which weakens attention toward alternative, nondrug goals and disrupts inhibitory control processes within the prefrontal cortex. This allows for automatic, implicit and habitual motivational processes (which are normally under inhibitory control) to exert a greater control over drug-seeking. In this model, the insula is still considered to be a part of the reflective system, as we have previously hypothesized, in that it plays a role in drug motivational processes that involve reflection upon the consequences of drug use, be they pleasurable or aversive (i.e. action-outcome contingencies). This system interacts with the impulsive system to influence goal-directed behavior. Specifically, when the insula is engaged by representations of the positive hedonic consequences of drug taking, it biases the impulsive system in the direction of drug use. When this occurs, it weakens representations of the negative hedonic consequences of drug use that normally bias the impulsive system in the direction of abstinence.

Thus, in our study (Naqvi et al. 2007), individuals who sustained insula damage may have been impaired in their ability to decide to quit smoking, but what predominated for them was a loss of the internal representation of the positive hedonic consequences of smoking, such that there was little conflict between these positive hedonic consequences and the rather salient and immediate negative repercussions of smoking, i.e. suffering from a stroke. These patients may have had intact mechanisms supporting the implicit, automatic motivation to smoke. However, such automatic motivational processes would have been necessarily interrupted in these patients by the fact that they were hospitalized after their brain injury, and thereby prohibited from smoking; as such, their habitual behavior would extinguish, and without the insular cortex input to re-sensitize the system, the extinguished behavior would become permanent. Thus, the effects of insula lesions in these patients may not have been to interrupt ongoing smoking behavior, but rather to make it easier to remain abstinent after returning home from the hospital. By this logic, a hypothetical patient who suffers from an insula lesion without being hospitalized may continue to smoke because the automatic, implicit motivation to smoke persists after insula damage. However, such a patient may find it easier to abstain when there is conflict between smoking and some other goal. This accords with Tiffany's model of drug urges (Tiffany and Conklin 2000), in which cueinduced urges become a motivating factor primarily when there is an obstacle to drug use.

Within such a framework, the insula may play a particular role in driving relapse, as opposed to motivating ongoing drug use in an individual who has not yet made a decision to quit (i.e. an individual in the pre-contemplative stage of change). This model also accords with a role for the insula in insight into drug use and its consequences, as proposed by Goldstein et al. (2009). In their model, the insula mediates the self-aware processes by which individuals reflect about their own agency in drug seeking. Conscious pleasure, cue-induced urges, and goal-directed drug-related decision-making, which we propose to be mediated by the insula, can be considered more basic processes that underlie insight.

A note on learning

The bodily effects of drug use become pleasurable through a learning process. The taste of alcohol, the nausea induced by opiates, the airway stimulation from smoking, are typically unpleasant to the drug-naïve individual. Over time, through repeated association with the direct CNS effects of drug use, these bodily effects acquire positive hedonic value. Rose and Levin (1991) has proposed for cigarette smoking that this learning process is a form of conditioned reinforcement, in which dopamine release elicited via the direct CNS actions of nicotine acts as the primary reinforcer. This model assumes that the facilitation of dopamine release is itself reinforcing, i.e. experienced as pleasurable. However, there is increasing evidence that dopamine release by itself is not a source of pleasure, and that dopamine plays

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a role in a neural plasticity that is not dependent upon reinforcement or pleasure (reviewed by Berridge and Robinson 1998). Such plasticity may lead to changes in the neural systems that process the hedonic value of interoceptive stimuli, such as the amygdala and OFC/VMPFC cortex. This plasticity may also be involved in encoding the interoceptive effects of drug use into longterm memory. Because the plasticity engendered by dopamine release is long-lasting, the interoceptive effects of drug taking remain pleasurable even in the absence of ongoing dopamine release. This would explain, for example, why the interoceptive effects of drug taking remain pleasurable even as tolerance develops to the CNS effects of the drug.

In a similar way, the environmental cues that are associated with drug use are initially motivationally neutral and over time come to elicit conscious cue-induced urges. This may occur through classical conditioning processes, in which the interoceptive effects of drug use act as unconditioned stimuli that become associated with conditioned environmental stimuli that predict and accompany drug use. Through repeated pairing with the bodily effects of drug use, these environmental stimuli activate representations of the bodily effects of drug use, “as if” the drug were being taken at that time. Dopamine release may play an in important role in this classical conditioning process by binding representations of the interoceptive effects of drug use with representations of environmental cues that predict their occurrence, in areas, such as the amygdala and the OFC/VMPFC, that are anatomically poised to integrate interoceptive and exteroceptive information. Dopamine release may also strengthen connections between the insula and the ventral striatum that function as a gate for the interoceptive effects of drug taking to affect motivated behavior. Whatever the specific learning processes involved, we believe that dopamine-mediated plasticity within brain systems that process the interoceptive effects of drug taking underlies a fundamental “switch” that occurs in addicted individuals: a switch from a state of finding the interoceptive effects of drug taking aversive and not particularly desirable to a state of finding these effects both pleasurable and attractive.

It is important to recall that none of the patients in our sample who sustained insula damage reported gross changes in their appetite or pleasure from eating, which is a behavior that is inherently pleasurable. One possibility is that motivated behaviors that are fundamental to survival and which are inherently pleasurable, such as eating, are supported by redundant neural mechanisms that are difficult to disrupt with a lesion in a single brain region. A further possibility is that the insula plays an especial role in motivated behaviors in which there is some conflict between that behavior and its negative consequences. For normal (i.e. non-binge) eating, there may be relatively little conflict between the pleasurable consequences of eating and the negative consequences of eating.

A question arises as to the role of the insula in so-called behavioral addictions, such as addiction to gambling. Functional imaging studies of gambling urges in pathological gamblers (Potenza et al. 2003; Crockford et al. 2005) have not shown activation in the insula. Of note, gambling does not provide the same kind of direct bodily stimulation that drug taking and naturally motivated behaviors provide [though it is known that winning and losing money under conditions of risk and uncertainty does elicit autonomic responses (Bechara et al. 1997; Bechara and Damasio 2002)]. Thus, the insula may only be involved in urges to engage in behaviors that have as their object a ritual that directly affects the bodily state. This highlights the possibility that the insula is critical for some, but not all, addictive behaviors.

Future directions

In this review, we have outlined a model for the role of the insula in drug addiction in which the representation of the interoceptive effects of drug use by the insula plays a central role in

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conscious pleasure, conscious cue-induced urge, and decision-making processes that involve weighing the positive and negative consequences of drug use. This model is a significant departure from traditional theories of drug addiction, which posit that the primary source of pleasure from drug use and therefore the goal of drug seeking behavior is the facilitation dopamine release from VTA neurons. Our view of addiction emphasizes conscious feelings, as well as the ambivalence about drug use that many drug addicted individuals feel, neither of which are taken into account by traditional animal models of drug addiction.

The model presented here makes several predictions for future research. First, it predicts that the interoceptive effects of drug use, even when experienced in the absence of direct CNS effects, will activate brain networks for conscious feelings and motivation, including the insula as well as its downstream targets in the orbitofrontal cortex and amygdala. It also predicts that such activity will be related to a number of factors that modulate the hedonic value derived from the interoceptive effects of drug use. These include the level of drug withdrawal; satiety obtained from interoceptive effects; the severity of dependence; and the effectiveness of ongoing treatments.

Given the effects of insula lesions on smoking addiction, it is possible that therapeutic strategies that are targeted at disrupting insula function will have a role in addiction treatment. The most obvious strategy would be to therapeutically lesion the insula to treat addiction. However, this strategy is both dangerous and impractical, given the important roles for the insula in normal functions, such as emotions, decision-making, language and attention [see the review by Ibanez et al. (2010) in this issue for a broader discussion of the cognitive and behavioral effects of insula lesions in humans]. A less invasive approach may involve modulating insula function, for example through deep brain stimulation or through repetitive transcranial magnetic stimulation (even though the insula may be too deep to be affected by rTMS, it may be possible to modulate insula function indirectly by stimulating afferent regions). Furthermore, future research may explore the effects of drugs that bind receptors in the insula and thereby modulate its function. For example, one may predict that modulation of D1 receptors within the insula influences the learning processes that promote the development and maintenance of addiction, or that modulation of CRH1 receptors within the insula influences the expression of withdrawal urges.

An implication of the theoretical perspective described in this review is that treatments for addiction that address the interoceptive effects of drug use are likely to be effective at modulating urges and also affecting decisionmaking processes that help addicted individuals avoid relapse. There are already studies that have shown that replacement of the interoceptive effects of cigarette smoking to be an effective means of promoting abstinence (Westman et al. 1995; Rezaishiraz et al. 2007). Future cognitive and behavioral therapies for addiction may attempt to “extinguish” memories for the pleasurable interoceptive effects of drug use, as a way to help drug addicted individuals “forget” the conscious urge to use drugs.

Acknowledgments

The research described in this article was supported by a grant from the National Institute on Drug Abuse (NIDA) R01 DA023051 (A.B.). The writing of this article was supported by grants from the National Institute of Mental Health (NIMH) R25 MH086466 (N.H.N.), and by the Leon Levy Resident Fellowship (N.H.N.).

References

Allen GV, et al. Organization of visceral and limbic connections in the insular cortex of the rat. J Comp Neurol. 1991; 311:1–16. [PubMed: 1719041]

NIH-PA Author Manuscript

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NIH-PA Author Manuscript

Allman JM, Tetreault NA, Hakeem AY, Manaye KF, Semendeferi K, Erwin JM, Goubert V, Hof PR. The von Economo neurons in frontoinsular and anterior cingulate cortex in great apes and humans. Brain Struc Func. 2010; 214(5–6) (this issue). 10.1007/s00429-010-0254-0

Arnow BA, et al. Brain activation and sexual arousal in healthy, heterosexual males. Brain. 2002; 125:1014–1023. [PubMed: 11960892]

Balleine BW, Dickinson A. The effect of lesions of the insular cortex on instrumental conditioning: evidence for a role in incentive memory. J Neurosci. 2000; 20:8954–8964. [PubMed: 11102506]

Bechara A. Decision making, impulse control and loss of willpower to resist drugs: a neurocognitive perspective. Nat Neurosci. 2005; 8:1458–1463. [PubMed: 16251988]

Bechara A, Damasio H. Decision-making and addiction (part I): impaired activation of somatic states in substance dependent individuals when pondering decisions with negative future consequences. Neuropsychologia. 2002; 40:1675–1689. [PubMed: 11992656]

Bechara A, Naqvi N. Listening to your heart: interoceptive awareness as a gateway to feeling. Nat Neurosci. 2004; 7:102–103. [PubMed: 14747831]

Bechara A, van der Kooy D. Opposite motivational effects of endogenous opioids in brain and periphery. Nature. 1985; 314:533–534. [PubMed: 2986002]

Bechara A, et al. Deciding advantageously before knowing the advantageous strategy. Science. 1997; 275:1293–1295. [PubMed: 9036851]

Berke JD, Hyman SE. Addiction, dopamine, and the molecular mechanisms of memory. Neuron. 2000; 25:515–532. [PubMed: 10774721]

Berridge KC, Robinson TE. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? Brain Res Brain Res Rev. 1998; 28:309–369. [PubMed: 9858756]

Berridge KC, Robinson TE. Parsing reward. Trends Neurosci. 2003; 26:507–513. [PubMed: 12948663]

Berthier M, et al. Asymbolia for pain: a sensory-limbic disconnection syndrome. Ann Neurol. 1988; 24:41–49. [PubMed: 3415199]

Bonson KR, et al. Neural systems and cue-induced cocaine craving. Neuropsychopharmacology. 2002; 26:376–386. [PubMed: 11850152]

Bossaerts P. Risk and risk prediction error signals in anterior insula. Brain Struc Func. 2010; 214(5–6) (this issue). 10.1007/s00429-010-0253-1

Brody AL, et al. Brain metabolic changes during cigarette craving. Arch Gen Psychiatry. 2002; 59:1162–1172. [PubMed: 12470133]

Brody AL, et al. Neural substrates of resisting craving during cigarette cue exposure. Biol Psychiatry. 2007; 62:642–651. [PubMed: 17217932]

Calder AJ, et al. Impaired recognition and experience of disgust following brain injury. Nat Neurosci. 2000; 3:1077–1078. [PubMed: 11036262]

Chikama M, et al. Insular cortical projections to functional regions of the striatum correlate with cortical cytoarchitectonic organization in the primate. J Neurosci. 1997; 17:9686–9705. [PubMed: 9391023]

Contreras M, et al. Inactivation of the interoceptive insula disrupts drug craving and malaise induced by lithium. Science. 2007; 318:655–658. [PubMed: 17962567]

Cox LS, et al. Evaluation of the brief questionnaire of smoking urges (QSU-brief) in laboratory and clinical settings. Nicotine Tob Res. 2001; 3:7–16. [PubMed: 11260806]

Craig AD. How do you feel? Interoception: the sense of the physiological condition of the body. Nat Rev Neurosci. 2002; 3:655– 666. [PubMed: 12154366]

Craig AD. How do you feel—now? The anterior insula and human awareness. Nat Rev Neurosci. 2009; 10:59–70. [PubMed: 19096369]

Craig AD. The sentient self. Brain Struc Func. 2010; 214(5–6) (this issue). 10.1007/s00429-010-0248-y

Critchley HD, Mathias CJ, Dolan RJ. Fear conditioning in humans: the influence of awareness and autonomic arousal on functional neuranatomy. Neuron. 2002; 33:653–663. [PubMed: 11856537]

Crockford DN, et al. Cue-induced brain activity in pathological gamblers. Biol Psychiatry. 2005; 58:787–795. [PubMed: 15993856]

NIH-PA Author Manuscript

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NIH-PA Author Manuscript

Cubero I, et al. Insular cortex lesions and taste aversion learning: effects of conditioning method and timing of lesion. Brain Res. 1999; 839:323–330. [PubMed: 10519056]

Damasio, AR. Descartes' Error: emotion, reason and the human brain. Putnam and Sons; New York: 1994.

Damasio, AR. The Feeling of What Happens: Body and Emotion in the Making of Consciousness. Harcourt; New York: 2000.

Dar R, Frenk H. Nicotine self-administration in animals: a reevaluation. Addict Res Theory. 2002; 10:545–579.

Dar R, Frenk H. Do smokers self-administer pure nicotine? A review of the evidence. Psychopharmacology (Berl). 2004; 173:18–26. [PubMed: 15004737]

de Araujo IE, et al. Human cortical responses to water in the mouth, and the effects of thirst. J Neurophysiol. 2003; 90:1865–1876. [PubMed: 12773496]

Del Parigi A, et al. Neuroimaging and obesity: mapping the brain responses to hunger and satiation in humans using positron emission tomography. Ann N Y Acad Sci. 2002; 967:389–397. [PubMed: 12079866]

Egan G, et al. Neural correlates of the emergence of consciousness of thirst. Proc Natl Acad Sci USA. 2003; 100:15241– 15246. [PubMed: 14657368]

Etter JF, Stapleton JA. Nicotine replacement therapy for longterm smoking cessation: a meta-analysis. Tob Control. 2006; 15:280– 285. [PubMed: 16885576]

Everitt BJ, Robbins TW. Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. Nat Neurosci. 2005; 8:1481–1489. [PubMed: 16251991]

Farrell MJ, et al. Unique, common, and interacting cortical correlates of thirst and pain. Proc Natl Acad Sci USA. 2006; 103:2416– 2421. [PubMed: 16461454]

Franklin TR, et al. Limbic activation to cigarette smoking cues independent of nicotine withdrawal: a perfusion fMRI study. Neuropsychopharmacology. 2007; 32:2301–2309. [PubMed: 17375140]

Garavan H. The insula and drug cravings. Brain Struc Func. 2010; 214(5–6) (this issue). 10.1007/s00429-010-0259-8

Garavan H, et al. Cue-induced cocaine craving: neuroanatomical specificity for drug users and drug stimuli. Am J Psychiatry. 2000; 157:1789–1798. [PubMed: 11058476]

Georgiadis JR, et al. Human brain activation during sexual stimulation of the penis. J Comp Neurol. 2005; 493:33–38. [PubMed: 16255007]

Goldstein RZ, et al. The neurocircuitry of impaired insight in drug addiction. Trends Cogn Sci. 2009; 13:372–380. [PubMed: 19716751]

Gowing L, et al. Alpha2 adrenergic agonists for the management of opioid withdrawal [update in Cochrane Database Syst Rev 2009;(2):CD002024; PMID: 19370574][update of Cochrane Database Syst Rev. 2003;(2):CD002024; PMID: 12804419]. Cochrane Database Syst Rev. 2004; (4):CD002024. [PubMed: 15495025]

Heatherton TF, et al. The Fagerstrom Test for nicotine dependence: a revision of the Fagerstrom Tolerance Questionnaire. Br J Addict. 1991; 86:1119–1127. [PubMed: 1932883]

Hudmon KS, et al. Validity of retrospective assessments of nicotine dependence: a preliminary report. Addict Behav. 2005; 30:613–617. [PubMed: 15718081]

Hurd YL, et al. D1 and D2 dopamine receptor mRNA expression in whole hemisphere sections of the human brain. J Chem Neuroanat. 2001; 22:127–137. [PubMed: 11470560]

Hurley KM, et al. Efferent projections of the infralimbic cortex of the rat. J Comp Neurol. 1991; 308:249–276. [PubMed: 1716270]

Ibanez A, Ezequiel G, Manes F. Clinical effects of insular damage in humans. Brain Struc Func. 2010; 214(5–6) (this issue). 10.1007/s00429-010-0256-y

James W. What is an emotion? Mind. 1884; 9:188–205.

Kampman KM, et al. Effectiveness of propranolol for cocaine dependence treatment may depend on cocaine withdrawal symptom severity. Drug Alcohol Depend. 2001; 63:69–78. [PubMed: 11297832]

Karama S, et al. Areas of brain activation in males and females during viewing of erotic film excerpts. Hum Brain Mapp. 2002; 16:1– 13. [PubMed: 11870922]

NIH-PA Author Manuscript

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NIH-PA Author Manuscript

Kilts CD, et al. The neural correlates of cue-induced craving in cocaine-dependent women. Am J Psychiatry. 2004; 161:233–241. [PubMed: 14754771]

Koob GF, Le Moal M. Drug addiction, dysregulation of reward, and allostasis. Neuropsychopharmacology. 2001; 24:97–129. [PubMed: 11120394]

Koob GF, et al. Neurobiological mechanisms in the transition from drug use to drug dependence. Neurosci Biobehav Rev. 2004; 27:739–749. [PubMed: 15019424]

Krettek JE, Price JL. Amygdaloid projections to subcortical structures within the basal forebrain and brainstem in the rat and cat. J Comp Neurol. 1978; 178:225–254. [PubMed: 627625]

Lee JH, et al. A functional magnetic resonance imaging (FMRI) study of cue-induced smoking craving in virtual environments. Appl Psychophysiol Biofeedback. 2005; 30:195–204. [PubMed: 16167185]

Levin ED, et al. Clinical trials using ascorbic acid aerosol to aid smoking cessation. Drug Alcohol Depend. 1993; 33:211–223. [PubMed: 8261886]

Lovero KL, et al. Anterior insular cortex anticipates impending stimulus significance. Neuroimage. 2009; 45:976–983. [PubMed: 19280711]

Manes F, et al. Neuropsychiatric effects of insular stroke. J Nerv Ment Dis. 1999; 187:707–712. [PubMed: 10665464]

McBride D, et al. Effects of expectancy and abstinence on the neural response to smoking cues in cigarette smokers: an fMRI study. Neuropsychopharmacology. 2006; 31:2728–2738. [PubMed: 16598192]

McClernon FJ, et al. Abstinence-induced changes in self-report craving correlate with event-related FMRI responses to smoking cues. Neuropsychopharmacology. 2005; 30:1940–1947. [PubMed: 15920499]

Medford N, Critchley HD. Conjoint activity of anterior insular and anterior cingulate cortex: awareness and response. Brain Struc Func. 2010; 214(5–6) (this issue). 10.1007/s00429-010-0265-x

Morecraft RJ, et al. Cytoarchitecture and neural afferents of orbitofrontal cortex in the brain of the monkey. J Comp Neurol. 1992; 323:341–358. [PubMed: 1460107]

Myrick H, et al. Differential brain activity in alcoholics and social drinkers to alcohol cues: relationship to craving. Neuropsychopharmacology. 2004; 29:393–402. [PubMed: 14679386]

Naqvi NH. The effects of lesions in the ventromedial prefrontal cortex and related areas on emotional responses to cigarette smoking. Neuroscience. 2006; 211

Naqvi, N., et al. Visceral and decision-making functions of the ventromedial prefrontal cortex. In: Zald, D.; Rauch, SL., editors. The orbitofrontaol cortex. Oxford University Press; Oxford: 2006.

Naqvi NH, Bechara A. The airway sensory impact of nicotine contributes to the conditioned reinforcing effects of individual puffs from cigarettes. Pharmacol Biochem Behav. 2005; 81:821–829. [PubMed: 15996724]

Naqvi NH, et al. Damage to the insula disrupts addiction to cigarette smoking. Science. 2007; 315:531–534. [PubMed: 17255515]

O'Brien CP, et al. Conditioning factors in drug abuse: can they explain compulsion? J Psychopharmacol. 1998; 12:15–22. [PubMed: 9584964]

Olausson H, et al. Unmyelinated tactile afferents signal touch and project to insular cortex. Nat Neurosci. 2002; 5:900–904. [PubMed: 12145636]

Paulozzi, LJ. Judiciary Subcommittee on Crime and Drugs. U.S. Department of Health and Human Services; 2008. Trends in unintentional drug overdose deaths. http://www.hhs.gov/asl/testify/2008/03/t20080312b.html

Paulus MP, et al. Neural activation patterns of methamphetamine- dependent subjects during decision making predict relapse. Arch Gen Psychiatry. 2005; 62:761–768. [PubMed: 15997017]

Pelchat ML, et al. Images of desire: food-craving activation during fMRI. Neuroimage. 2004; 23:1486–1493. [PubMed: 15589112]

Peto R, et al. Mortality from tobacco in developed countries: indirect estimation from national vital statistics. Lancet. 1992; 339:1268–1278. [PubMed: 1349675]

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Phan KL, et al. Functional neuroanatomy of emotion: a metaanalysis of emotion activation studies in PET and fMRI. Neuroimage. 2002; 16:331–348. [PubMed: 12030820]

Potenza MN, et al. Gambling urges in pathological gambling: a functional magnetic resonance imaging study. Arch Gen Psychiatry. 2003; 60:828–836. [PubMed: 12912766]

Rezaishiraz H, et al. Treating smokers before the quit date: Can nicotine patches and denicotinized cigarettes reduce cravings? Nicotine Tob Res. 2007; 9:1139–1146. [PubMed: 17978987]

Robinson TE, Berridge KC. Incentive-sensitization and addiction. Addiction. 2001; 96:103–114. [PubMed: 11177523]

Rolls ET, Rolls ET. Taste and related systems in primates including humans. Chem Senses. 2005; 30(Suppl 1):i76–i77. [PubMed: 15738204]

Rolls ET, Sienkiewicz ZJ, Yaxley S. Hunger modulates the responses to gustatory stimuli of single neurons in the caudolateral orbitofrontal cortex of the macaque monkey. Eur J Neurosci. 1989; 1:53–60. [PubMed: 12106174]

Rose JE, Levin ED. Inter-relationships between conditioned and primary reinforcement in the maintenance of cigarette smoking. Br J Addict. 1991; 86:605–609. [PubMed: 1859927]

Rosenblum K, et al. Taste memory: the role of protein synthesis in gustatory cortex. Behav Neural Biol. 1993; 59:49–56. [PubMed: 8442732]

Rosenblum K, et al. Modulation of protein tyrosine phosphorylation in rat insular cortex after conditioned taste aversion training. Proc Natl Acad Sci USA. 1995; 92:1157–1161. [PubMed: 7862652]

Sanchez MM, et al. Autoradiographic and in situ hybridization localization of corticotropin-releasing factor 1 and 2 receptors in nonhuman primate brain. J Comp Neurol. 1999; 408:365–377. [PubMed: 10340512]

Sehlmeyer C, et al. Human fear conditioning and extinction in neuroimaging: a systematic review. PLoS ONE. 2009; 4:e5865. (electronic resource). [PubMed: 19517024]

Sell LA, et al. Activation of reward circuitry in human opiate addicts. Eur J Neurosci. 1999; 11:1042–1048. [PubMed: 10103096]

Small D. Taste representation in the human insula. Brain Struc Func. 2010; 214(5–6) (this issue). 10.1007/s00429-010-0266-9

Spiess, M.; Fallow, D. Drug-Related Crime Report. 2000. Retrieved May 11, 2009, from Office of National Drug Control Policy Web site: http://www.whitehousedrugpolicy.gov/publications/factsht/crime/index.html

Stinson FS, DeBakey SF. Alcohol-related mortality in the United States, 1979–1988. Br J Addict. 1992; 87:777–783. [PubMed: 1591529]

Stoleru S, et al. Neuroanatomical correlates of visually evoked sexual arousal in human males. Arch Sex Behav. 1999; 28:1–21. [PubMed: 10097801]

Tapert SF, et al. fMRI BOLD response to alcohol stimuli in alcohol dependent young women. Addict Behav. 2004; 29:33–50. [PubMed: 14667419]

Tiffany ST. A cognitive model of drug urges and drug-use behavior: role of automatic and nonautomatic processes. Psychol Rev. 1990; 97:147–168. [PubMed: 2186423]

Tiffany ST. Meta-analysis of cue-reactivity in addiction research. Addiction. 1999; 94:327–340. [PubMed: 10605857]

Tiffany ST, Conklin CA. A cognitive processing model of alcohol craving and compulsive alcohol use. Addiction. 2000; 95(Suppl 2):S145–S153. [PubMed: 11002909]

Tiffany ST, et al. Effects of transdermal nicotine patches on abstinence-induced and cue-elicited craving in cigarette smokers. J Consult Clin Psychol. 2000; 68:233–240. [PubMed: 10780123]

Vorel SR, et al. Insula damage and quitting smoking. Science. 2007; 317:318–319. author reply 318–319. [PubMed: 17641181]

Wang GJ, et al. Regional brain metabolic activation during craving elicited by recall of previous drug experiences. Life Sciences. 1999; 64:775–784. [PubMed: 10075110]

Wang GJ, et al. Exposure to appetitive food stimuli markedly activates the human brain. Neuroimage. 2004; 21:1790–1797. [PubMed: 15050599]

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Wang Z, et al. Neural substrates of abstinence-induced cigarette cravings in chronic smokers. J Neurosci. 2007; 27:14035–14040. [PubMed: 18094242]

Wang GJ, et al. Gastric distention activates satiety circuitry in the human brain. Neuroimage. 2008; 39:1824–1831. [PubMed: 18155924]

Westman EC, et al. Airway sensory replacement combined with nicotine replacement for smoking cessation. A randomized, placebo-controlled trial using a citric acid inhaler. Chest. 1995; 107:1358–1364. [PubMed: 7750331]

Westman EC, et al. Dissociating the nicotine and airway sensory effects of smoking. Pharmacol Biochem Behav. 1996; 53:309– 315. [PubMed: 8808137]

Wexler BE, et al. Functional magnetic resonance imaging of cocaine craving. Am J Psychiatry. 2001; 158:86–95. [PubMed: 11136638]

Wikler A. Recent progress in research on the neurophysiological basis of morphine addiction. Am J Psychiatry. 1948; 105:329– 338. [PubMed: 18890902]

Wise RA, Bozarth MA. A psychomotor stimulant theory of addiction. Psychol Rev. 1987; 94:469–492. [PubMed: 3317472]

Yaxley S, et al. The responsiveness of neurons in the insular gustatory cortex of the macaque monkey is independent of hunger. Physiol Behav. 1988; 42:223–229. [PubMed: 3406148]

Zito KA, et al. The dopamine innervation of the visceral cortex mediates the aversive effects of opiates. Pharmacol Biochem Behav. 1988; 30:693–699. [PubMed: 3211979]

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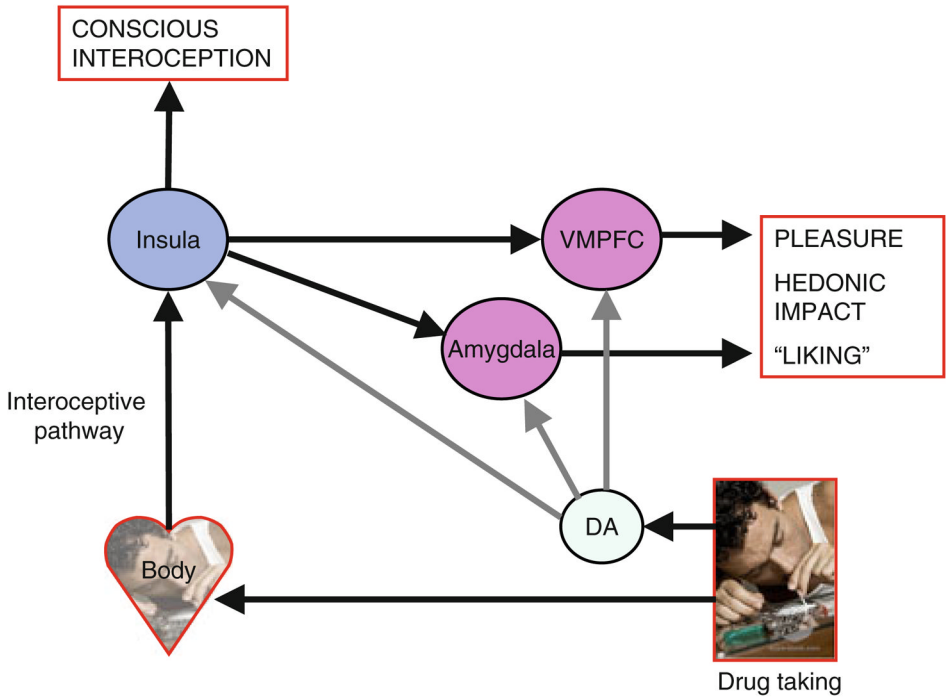

Fig. 1.

A model for the role of the insula in deriving conscious pleasure from the interoceptive effects of drug taking. Interoceptive effects are signaled in the insula via a dedicated thalamocortical pathway. The representation of these interoceptive effects in the insula gives rise to conscious awareness of interoceptive effects, which allows, for example, the ability to perform sensory discrimination. This representation is then fed to regions, such as the amygdala and the OFC/VMPFC, that translate the interoceptive effects of drug use into conscious pleasure. Dopamine (DA) release in these regions from VTA neurons, facilitated by the direct CNS effects of drug taking, modulates this conscious pleasure. Dopamine may also be important for learning processes that cause the interoceptive effects to become pleasurable in the first place

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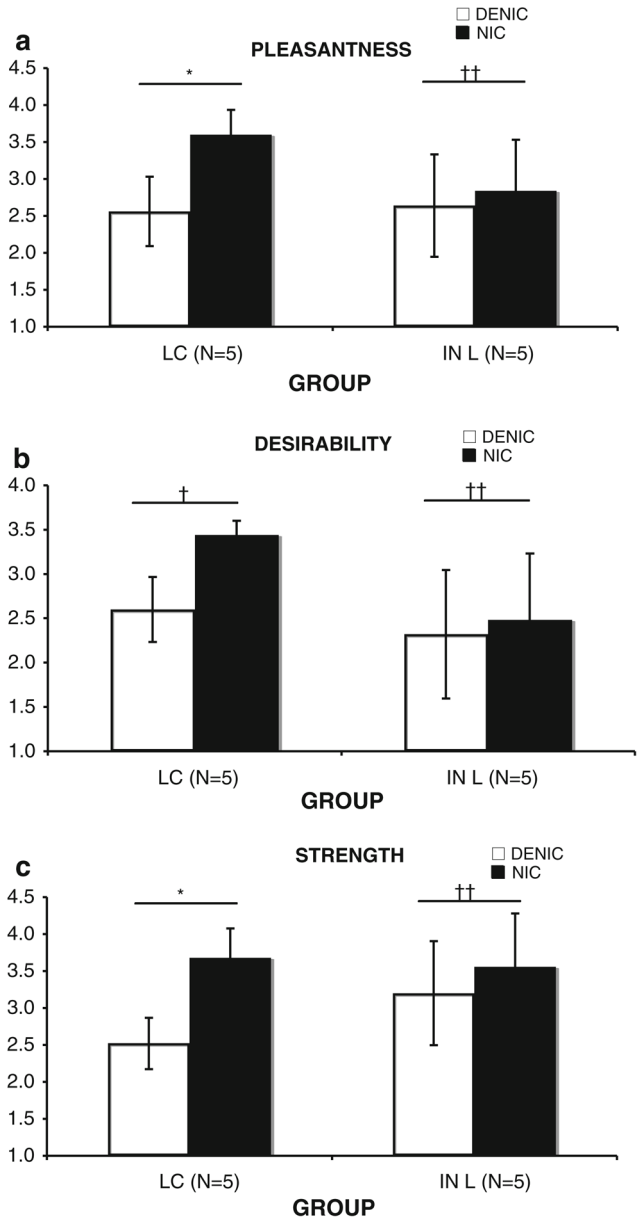

Fig. 2.

The effects of left insula lesions on hedonic discrimination of the sensory impact of nicotine. In this experiment, subjects with left insula lesions (IN L) and comparison subjects with lesions in noninsula regions (LC) took individual puffs from cigarettes that contained either tobacco with nicotine (NIC) or tobacco in which nicotine had been removed through genetic modification (DENIC). Nicotinzed puffs elicit stronger airway sensations than denicotinized puffs. Self-reports of pleasantness, desirability and strength were recorded within 5 s of inhalation of the puffs, to ensure that differences between puffs could not be attributed to the direct CNS effects of nicotine. Lesioned comparison subjects found puffs with nicotine to be more pleasurable, desirable, and stronger than puffs without nicotine. Subjects with left insula lesions failed to make these discriminations, demonstrating a role for conscious awareness of the interoceptive effects of smoking, as well as in the conscious experience of pleasure that is derived from these effects. $^{*}P < 0.05$; $^{\dagger}P = 0.05$; $^{\dagger\dagger}P > 0.05$

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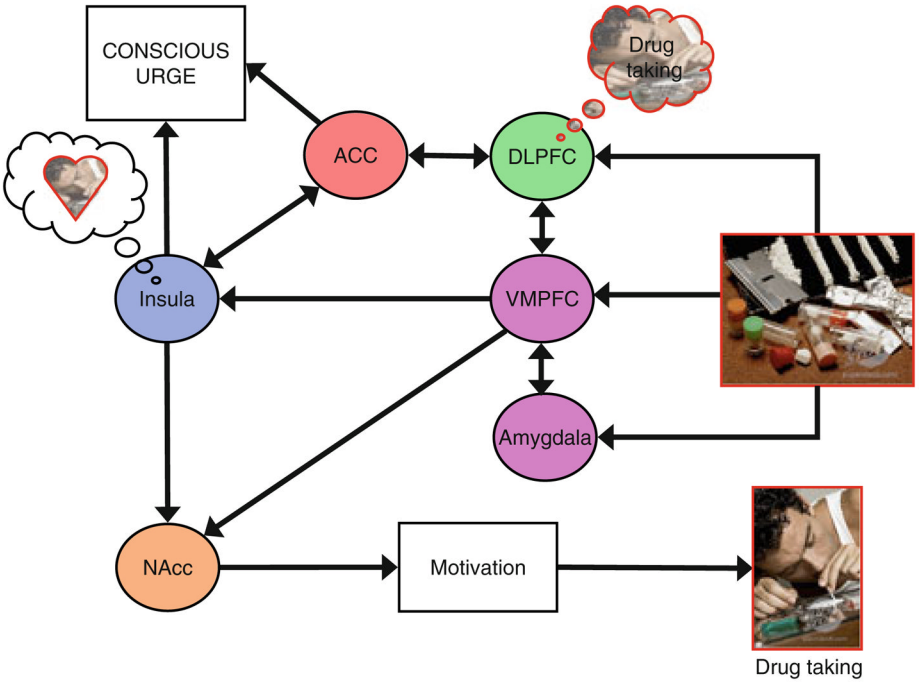

Fig. 3.

A model for the role of the insula in cue-induced drug urges. Exposure to environmental drug cues leads to retrieval of a representation of the interoceptive effects of drug taking from longterm memory. Regions that receive information about the presence of cues in the external world (the amygdala and the OFC/VMPFC) and regions that recall information about drug cues from long-term memory and maintain this information in working memory (the OFC/VMPFC and the DLPFC) trigger the activation of this representation within the insula. This representation, when integrated with representations of drug cues within the environment in regions such as the ACC, contributes to a conscious feeling of urge that is "about" a specific drug taking ritual, with specific interoceptive effects. Representations of this drug taking ritual occupy working memory. The connections between the insula and the ventral striatum (VS) motivates drug-seeking behaviors that are specific for a particular drug taking ritual

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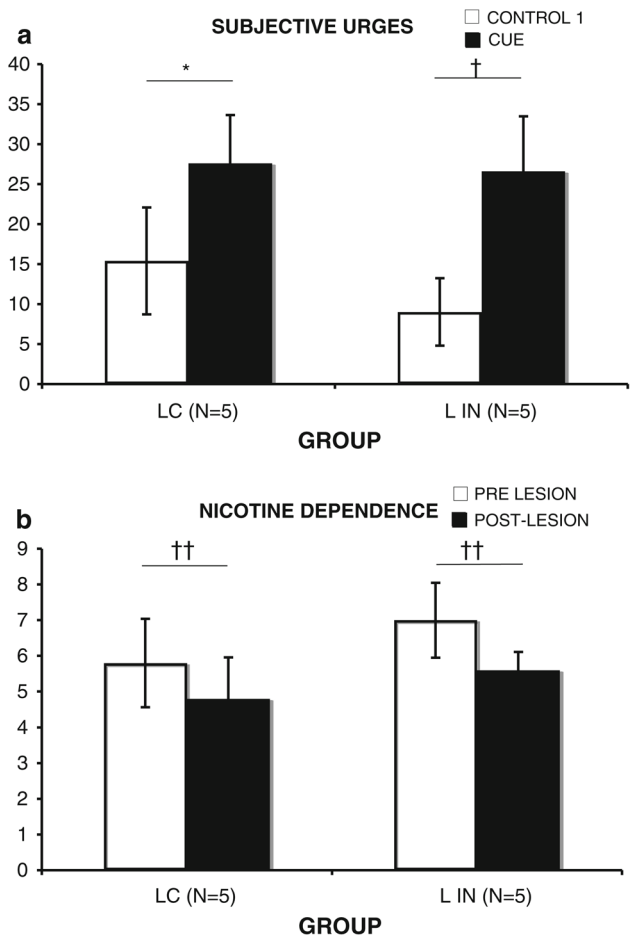

Fig. 4.

Effects of left insula lesions on cue-induced urges and the severity of smoking addiction. Both lesioned comparison subjects (LC) and left insula lesioned subjects (L IN) showed an increase in urges in response to a smoking cue, compared to a control cue. Neither lesioned comparison subjects nor left insula lesioned subjects showed a reduction in the severity of nicotine dependence from preto post-lesion onset. All subjects were patients who continued to smoke after lesion onset. The results suggest patients who continue to smoke after damage in the left insula do not experience a reduction in their smoking urges. *QSU-B* Brief Questionnaire of Smoking Urges (Cox et al. 2001); *FTND* Fagerstrom Test for Nicotine Dependence (Heatherton et al. 1991; Hudmon et al. 2005); $^{*}P < 0.05$; $^{\dagger}P = 0.05$; $^{\dagger\dagger}P > 0.05$

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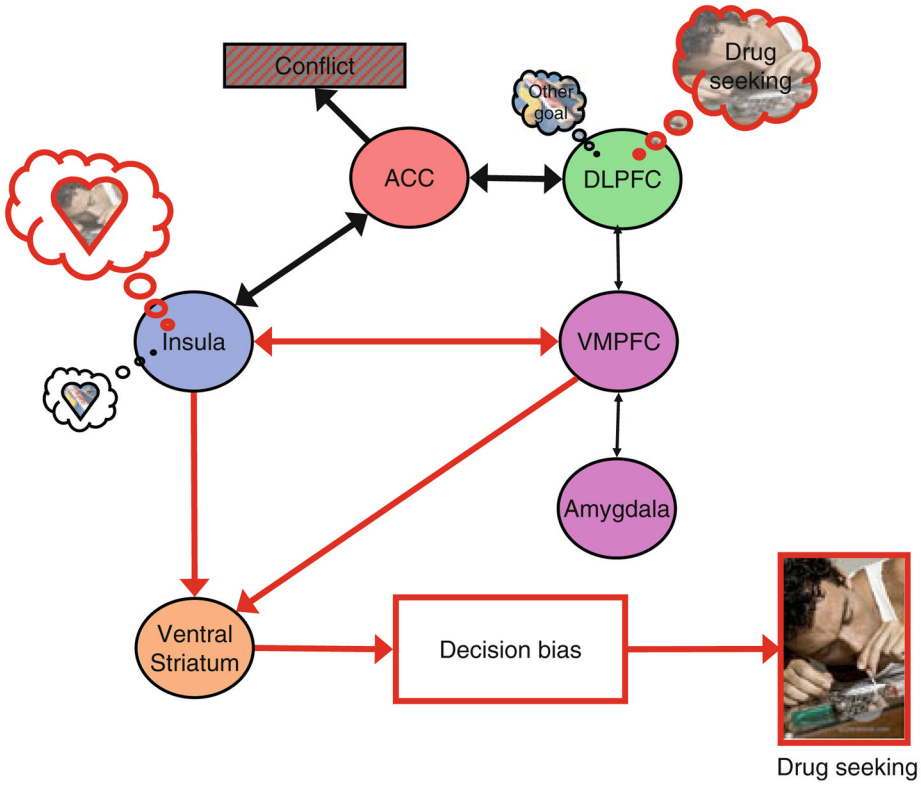

Fig. 5.

A model for the decision to relapse. When confronted with situations that typically elicit drug seeking and feelings of urge, the addicted individual recalls the interoceptive effects of drug taking (similar to the process of cue-induced drug urge). In individuals who are attempting to abstain from drug taking, representations of negative consequences of drug use (e.g. losing a job, dropping out of school) are also recalled in interoceptive terms. The representation of the interoceptive effect of drug use "win out" over the representations of the interoceptive effects of the adverse consequences of drug use. This is manifested in a greater attentional allocation to the goal of drug seeking, as well as a biasing of behavior towards drug seeking. Successful avoidance of relapse, then, may involve suppressing representations of the pleasurable interoceptive effects of drug use, along with enhancing representations of the negative interoceptive effects of the adverse consequences of drug use

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Table 1

Functional neuroimaging studies of drug urges showing insula activitation

Study	Drug	Insula	OFC/VMPFC	ACC	DLPFC	Amygdala	VS	HF
McBride et al. (2006)	Cigarettes	L	L	L,R	L[a]			
Franklin et al. (2007)	Cigarettes	L	R		L[a]	L,R	L,R	L,R
Brody et al. (2002)	Cigarettes	L[a],R[a]	L[a],R[a]	L,R	L[a],R[a]	L		
Brody et al. (2007)	Cigarettes	L[a],R[a]		L[a],R[a]	L[a]			
McClernon et al. (2005)	Cigarettes	L,R		L[a],R[a]	L[a],R[a]			
Lee et al. (2005)	Cigarettes	R	L	L	R			
Wang et al. 2007	Cigarettes	R[a]	R[a]	R[a]	R[a]	R[a]	R[a]	L[a],R[a]
Kilts et al. (2004)	Cocaine	L		R		L,R	R	
Bonson et al. (2002)	Cocaine	L[a]	L[a]		R[a]	L[a]		
Kilts et al. (2004)	Cocaine	L[a],R[a]	L[a],R[a]	L		L,R	R	
Wang et al. (1999)	Cocaine	L,R[a]	L[a],R[a]					
Garavan et al. (2000)	Cocaine	R		L	L,R			
Wexler et al. (2001)	Cocaine	R		L,R	L			
Myrick et al. (2004)	Alcohol	L,R	L[a],R[a]	L[a],R			L[a],R	L
Tapert et al. (2004)	Alcohol	L,R		L	L			
Sell et al. (1999)	Heroin	L	L	L,R				

In nearly all of these studies, subjects are passively exposed to drug-associated environmental cues, i.e. no behavior is executed, while brain activity is measured, and then asked to rate their subjective urges. Note that other cortical regions, including the OFC/VMPFC, DLPFC and ACC are frequently activated along with the insula, and that activations in all of these regions are often correlated with subjective urges. Also, note the relative paucity of activation in subcortical regions

OFC/VMPC orbitofrontal cortex/ventromedial prefrontal cortex, *ACC* anterior cingulate cortex, *DLPFC* dorsolateral prefrontal cortex, *VS* ventral striatum, *HF* hippocampal formation

[a]Regions in which brain activity was positively correlated with subjective urges