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The insula: a critical neural substrate for craving and drug seeking under conflict and risk

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Drug addiction is characterized by the inability to control drug use when it results in negative consequences or conflicts with more adaptive goals. Our previous work showed that damage to the insula disrupted addiction to cigarette smoking—the first time that the insula was shown to be a critical neural substrate for addiction. Here, we review those findings, as well as more recent studies that corroborate and extend them, demonstrating the role of the insula in (1) incentive motivational processes that drive addictive behavior, (2) control processes that moderate or inhibit addictive behavior, and (3) interoceptive processes that represent bodily states associated with drug use. We then describe a theoretical framework that attempts to integrate these seemingly disparate findings. In this framework, the insula functions in the recall of interoceptive drug effects during craving and drug seeking under specific conditions where drug taking is perceived as risky and/or where there is conflict between drug taking and more adaptive goals. We describe this framework in an evolutionary context and discuss its implications for understanding the mechanisms of behavior change in addiction treatments.

Keywords: insula; addiction; risk; craving; drug seeking

Background

Addiction, defined as compulsive drug use despite significant negative consequences,[1] is a major cause of morbidity and mortality globally (here we use the term *drug* to encompass all addictive substances, including alcohol). Although there are some moderately effective treatments for addiction, there is no cure. Identifying specific neural targets for addiction treatments should help improve their efficacy and may someday lead to a cure.

There has been an explosion of research on the neuroscience of addiction over the last three decades. Much of this work has implicated the striatum (both ventral and dorsal), along with its inputs from the ventromedial prefrontal cortex, the amygdala, and the mesolimbic dopamine system, in a variety of appetitive motivational processes that drive drug seeking and drug taking.[2–4] A parallel line of research has highlighted the role of impairments in prefrontal cortical systems that govern impulse-control and decision-making processes, which normally rein in drug seeking and drug taking.[5–9] The broad clinical implication of this body of research is that interventions that downmodulate the function of motivational systems or that enhance the functioning of control systems should reduce addictive behavior.[10] Despite this remarkable progress, no effective treatments have been derived from our increasingly sophisticated understanding of the brain basis of addiction.

In 2007, we discovered that damage to the human insula, a brain region that had until that point been largely overlooked by addiction researchers, led to an abrupt and profound disruption of addiction to cigarette smoking.[11] Although this finding was immediately sensationalized as evidence of a "cure" for addiction,[12,13] its actual clinical relevance

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lay in stimulating questions about *why* the insula should play such a critical role in addiction. Since the publication of our findings, there have been an increasing number of studies, in both humans and animals, addressing specific mechanistic hypotheses about the functions of the insula in addiction. In this review, we begin by summarizing our initial findings on the effects of insula lesions on smoking behavior, as well as more recent human lesion studies that replicate and extend our work. We then review functional imaging and animal studies examining the role of the insula in (1) appetitive motivational processes that drive addictive behavior, (2) interoceptive functions that are relevant to drug addiction, and (3) impulse-control and decision-making processes that modify addictive behavior according to conflicting goals and negative consequences. We then present a model that integrates these seemingly disparate aspects of insula function, focusing on the role of the insula in subjective craving and drug seeking in the face of risk and conflict. Finally, we discuss how the insula, by mediating these functions, may be a target for addiction treatments.

The effects of insula damage on addiction to cigarette smoking

Before our 2007 study, we observed that a number of functional-imaging studies reported that exposure to drug cues activated the insula, and that insula activity was correlated with self-reported cravings (reviewed in Ref. 14). At that time, we were interested in the insula as a neural substrate for conscious emotional feelings and decision making, as set forth in Damasio's somatic-marker framework.[15,16] According to this framework, the insula was part of a network of brain regions that represented bodily states associated with emotions, a process that gave rise to conscious emotional feelings and also biased risky decisions with emotional outcomes toward advantageous choices. We viewed cue-induced drug craving as an emotion. Similar to other emotions, such as anger, fear, disgust, and sadness, cue-induced craving was triggered by motivationally relevant stimuli; it was associated with autonomic physiological responses, it was experienced as a highly salient subjective feeling, and it correlated with neural activity in the insula. We chose to examine the effects of insula lesions on addiction to cigarette smoking because of the high prevalence of cigarette smoking, especially among patients with brain damage resulting from stroke. We hypothesized that if the insula was critical for emotional feelings in general, and if cue-induced cigarette craving was one kind of emotional feeling, then insula lesions should disrupt craving. Furthermore, if craving maintained addiction to smoking, then insula lesions should make it easier to stop smoking and should also reduce the likelihood of relapse.

In our study,[11] we retrospectively examined the effects of insula damage on the likelihood of two outcomes: (1) quitting smoking after brain damage and (2) undergoing a disruption of smoking addiction, which we operationalized as not only quitting but being able to do so immediately, easily, without relapsing, and without a persistent urge to smoke. We chose these outcomes because, while many smokers would have successfully quit smoking due to increased health concerns around smoking after their brain injury, only smokers with damage in brain regions critical for addiction would have been able to quit easily, immediately, without relapsing, and without craving. According to this classification, patients who were designated as having undergone a disruption of smoking addiction were a subset of the patients who quit smoking. Furthermore, patients who continued to smoke after their brain injury were assumed to have no disruption of smoking addiction.

We identified 19 patients with insula lesions (13 with left-sided lesions and six with right-sided lesions), along with 50 lesion-comparison patients with damage in areas both adjacent and nonadjacent to the insula (the location of the insula, along with its anatomical subdivisions and major inputs/outputs, is shown in Fig. 1). Patients in both groups were smoking on average more than a pack per day at the time of lesion onset. In both groups, most of the lesions were caused by stroke. We found that patients with insula lesions, either on the right or left side, were somewhat more likely to quit smoking after lesion onset than comparison patients, though this was not a statistically significant difference. We then restricted our analysis to patients who actually quit after lesion onset, examining the frequency of disruption of smoking addiction among these patients. We found that 5/5 patients with right insula lesions and 7/8 patients with left insula lesions who quit after lesion onset underwent a disruption of smoking addiction, compared to 4/19 comparison patients who quit after lesion onset (right

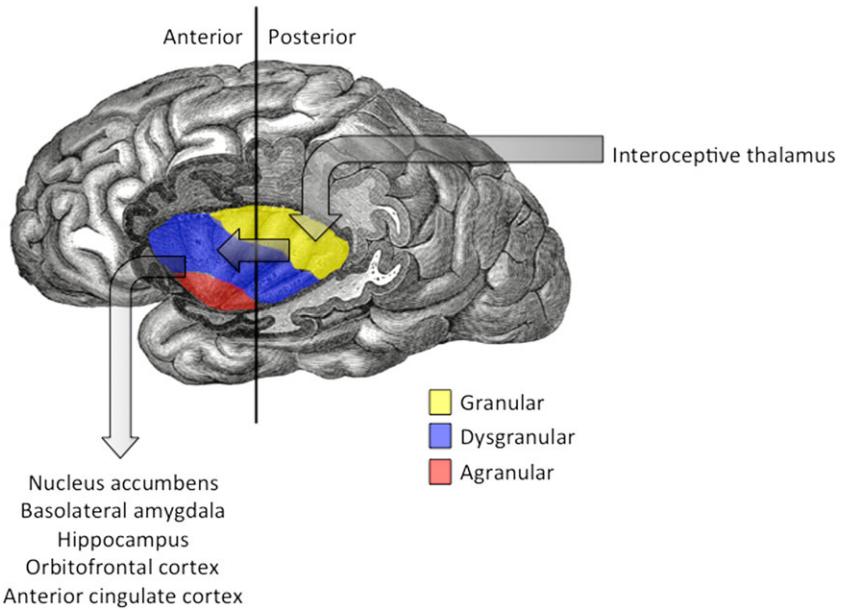

Figure 1. **The insula, its anatomical subdivisions, and major inputs/outputs. Adapted from Refs. 121–123.**

insula vs. comparison group: odds ratio (OR) = 6.55, $\chi^2 = 7.76$, and $P = 0.005$; left insula vs. comparison group: OR = 7.19, $\chi^2 = 10.06$, and $P = 0.002$; all controlled for lesion size; Fig. 2). None of the patients in either group reported changes in their motivation to eat or their enjoyment from food. We speculated that insula lesions disrupted conscious craving, which made it easier to quit and reduced the likelihood of relapse. Interestingly, one of the patients with insula lesions whom we interviewed extensively (patient *N*) described how his "body forgot the urge to smoke." In addition, he reported that smoking, which used to be pleasurable in his dreams, was now something that he found disgusting in his dreams, as if it had become decoupled from its positive hedonic value in his imagination.

Suñer-Soler *et al.*[17] addressed one of the major limitations of our study by examining the effects of insula lesions on smoking addiction prospectively. They compared patients with insula strokes to patients with noninsula strokes, all smoking regularly at the time of their stroke. They found that insula strokes increased the odds of quitting more than fivefold, compared to noninsula strokes. They also found a strong though nonsignificant trend toward insula strokes increasing the likelihood of undergoing a disruption of smoking addiction, as we originally defined it. They also examined the level of motivation for quitting both before the stroke (retrospectively) and at 3–6 months and 1 year poststroke. They reported that 85.5% of all the patients in the study sample were *precontemplative* (not thinking about quitting) at stroke onset, with no significant difference between the groups. They then found that significantly more patients with insula strokes were in the *maintenance* phase of motivation (i.e., able to sustain abstinence) at both 3–6 months and 1 year poststroke, compared to patients with noninsula strokes. They also found that having an intention to quit smoking before the stroke predicted the likelihood of quitting after stroke, though they did not examine the interaction between this effect and lesion location. This study showed an effect of insula lesions on quitting, whereas our study did not. Furthermore, it showed only a trend toward an effect of insula lesions on the disruption of addiction outcome, whereas we found highly significant effects. Notwithstanding these differences, the results are consistent with an effect of insula lesions on motivational processes that impede quitting.

We recently performed a study[18] in which we prospectively examined the combined effects of insula lesions and basal ganglia lesions on smoking behavior. The basal ganglia, which include the nucleus accumbens, caudate, putamen, and globus pallidus,

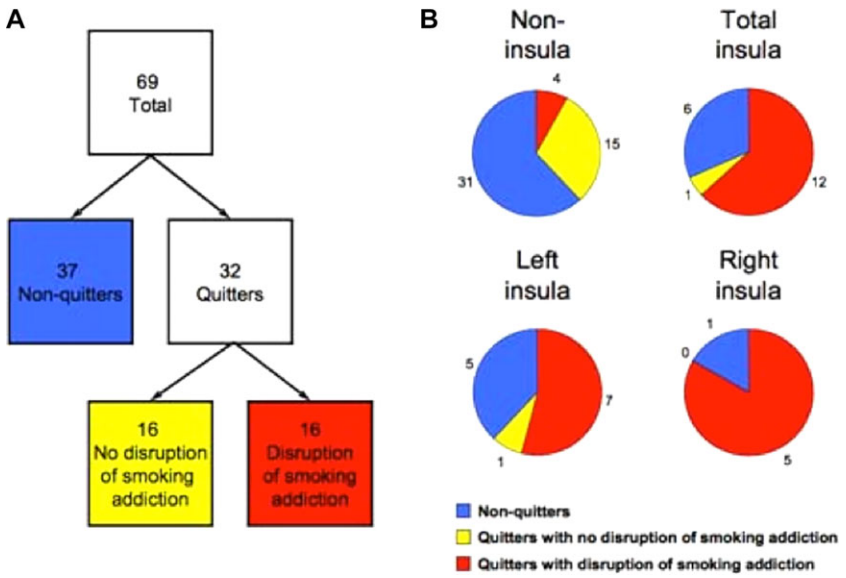

Figure 2. **Analysis of patients who did and did not quit smoking on the basis of lesion localization with respect to insula. Results from Ref. 11.**

are anatomically adjacent to the insula and, due to a shared vascular supply, are frequently damaged by strokes that involve the insula. We compared the effects of lesions that affected the basal ganglia alone ($n = 9$) to lesions that affected both the basal ganglia and insula ($n = 8$), along with comparison lesions that included neither the insula nor the basal ganglia ($n = 46$). As in our original 2007 study, we examined the effects of these lesions on the likelihood of two binary outcomes: (1) quitting smoking after lesion onset and (2) disruption of smoking addiction after lesion onset (being able to quit smoking easily, immediately, without relapsing, and without craving). We also examined the effects of the lesions on a continuous measure of the severity of nicotine dependence, the score on the Fagerström Test for Nicotine Dependence (FTND). We found that lesions to the basal ganglia alone were associated with an increased likelihood of quitting smoking and with greater reduction in FTND scores, compared to comparison lesions. Furthermore, we found that lesions that included both the basal ganglia and the insula led to an even greater likelihood of quitting smoking and even greater reductions of FTND score, compared to lesions of the basal ganglia alone. However, there were no effects of either basal ganglia lesions or of combined basal ganglia and insula lesions on the disruption of smoking addiction outcome. This may have been due to a small sample size, combined with the fact that the FTND score was a continuous measure that could be assessed in all patients, whereas disruption of smoking was a dichotomous outcome that could only be applied to patients who quit. Nevertheless, these findings showed that the basal ganglia, broadly defined, play an important role in addictive behavior, which is consistent with previous animal studies,[2] as well as case reports of human addicts who quit drug use after basal ganglia damage.[19] Furthermore, they suggest additive effects when basal ganglia lesions are combined with insula lesions, providing additional support for the role of the insula in addiction.

Bienkowski *et al.*[20] performed the only human lesion study that contradicted our results. They found that patients with insula strokes were not more likely to quit smoking than patients with non-insula strokes. They also found that none of the patients who quit smoking after a stroke—in any lesion group—underwent a disruption of smoking addiction, as we had originally defined it. One explanation for this discrepancy is that the Bienkowski *et al.* study took place in Poland, which has one of the highest cigarette consumption rates in the world despite some of the most aggressive antismoking measures,[21,22] and where nearly half of smokers who are prompted to quit because of health

problems related to smoking do not perceive the link between the two.[23] As we discuss in more detail later, the perception that smoking has negative consequences may be an important psychological factor mediating the effects of insula lesions on smoking addiction.

The insula as an appetitive motivational system in addiction

Since our initial 2007 study, a number of meta-analyses of functional-imaging studies have confirmed the insula's involvement in cue-induced drug craving, which is an appetitive emotion that promotes drug use. Kuhn *et al.*[24] examined studies across a variety of drugs of abuse and found that the right posterior insula was activated by cocaine cues, but not by nicotine or alcohol cues. They also found that self-reported craving was correlated with right anterior insula activity for nicotine, but not for cocaine or alcohol. Schacht *et al.*[25] found that alcohol cues elicited greater activity in the right insula than control stimuli, and that this difference was larger for alcohol-dependent drinkers than for social drinkers. Engelmann *et al.*[26] found that smoking cues elicited activation in the left posterior insula. Chase *et al.*[27] examined cue reactivity across multiple substances, and found no cue-elicited activation in the insula, despite the fact that many of the individual studies included in the meta-analysis did reveal cue-elicited insula activity. This may have been because the method used to aggregate results across studies underreported activations in large and functionally heterogeneous regions, such as the insula.

Although functional imaging studies provide evidence that the insula is involved in self-reported craving, they do not actually prove that the insula plays a role in driving addictive behavior in real life. Thus, a number of functional-imaging studies have shown relationships between cue-elicited insula activity and clinical variables related to addiction severity and treatment outcome. Janes *et al.*[28] showed that, in treated, abstinent smokers, cue-elicited activity in both the right and left anterior insula predicted *slips* (nonrelapse smoking episodes). They also showed that cue-elicited anterior insula activity correlated bilaterally with interference effects in a smoking Stroop behavioral paradigm, suggesting a relationship between anterior insula function and an inability to disengage attention from smoking-related information when this conflicts with goal-relevant task demands. Claus *et al.*[29] found that nicotine-dependence severity was positively correlated with cue-elicited activity in the left insula, along with cue-elicited functional connectivity between the left insula and a number of regions involved in emotion, motivation, and cognitive control, such as the right insula, the orbitofrontal cortex (OFC), the dorsal anterior cingulate cortex (ACC), and the subgenual ACC. The same group[30] also found that cue-elicited activity in the right insula correlated with the severity of alcohol dependence. A few studies have revealed moderating effects of genes that predispose to addiction on cue-elicited insula activity. For example, Blaine *et al.*[31] found that alcohol-dependent patients who possessed higher-risk isoforms of the tachykinin receptor 1, which is involved in stress signaling, had increased cue-elicited activity in the anterior and posterior insula bilaterally. Janes *et al.*[32] found that smokers with a lower-risk allele of the $\alpha 5$ subunit of the nicotinic acetylcholine receptor had enhanced cue-elicited neural activity in the insula bilaterally.

Animal models of drug motivation allow for anatomically targeted manipulation of insula functions coupled with detailed behavioral analysis, providing evidence for the role of the insula in specific motivational functions that may drive addiction. Studies in rodents,[33–39] which we summarize in Table 1, are heterogeneous with respect to the specific insular subregions targeted, the method of manipulation of insula function, and the behavioral assays used to assess the effects of the manipulations. However, a number of themes emerge from examining these studies together. First, they all show that manipulations that disrupt insula functioning reduce drug-seeking behavior, which is broadly consistent with the effects of insula lesions in humans. Second, there appears to be a dissociation of function between the posterior (granular) insula and the anterior (agranular) insula: whereas the posterior insula is necessary for registering the reinforcement value of drugs (as measured in self-administration paradigms) and for the learning of drug-context associations (as measured by the acquisition of conditioned place preference), the anterior insula is necessary for the retrieval and reconsolidation of drug-context associations (as measured by delayed recall of conditioned place preference). Third, whereas

Table 1. Rodent studies of the role of the insula in addictive behavior

Study	Drug	Insular region	Manipulation	Behavioral effects
Contreras *et al.*[34]	Amphetamine	Posterior insula	Lidocaine injection	Reversibly abolished CPP Reversibly abolished lithium-induced malaise
Hollander *et al.*[36]	Nicotine	Anterior and posterior insula combined	Hypocretin receptor blockade	Reduced self-administration
Forget *et al.*[35]	Nicotine	Posterior insula	GABA agonist inactivation	Reduced self-administration Prevented drug- and cue-induced reinstatement of self-adminstration
Scott and Hiroi[37]	Nicotine	Anterior and posterior insula combined	Excitotoxic lesion	Disrupted nicotine-cue approach Spared withdrawal-cue avoidance
Contreras *et al.*[33]	Amphetamine	Anterior insula	Protein synthesis inhibition	Abolished retrieval of CPP
		Posterior insula	Protein synthesis inhibition	No effect on CPP
Pushparaj *et al.*[38]	Nicotine	Posterior	Electrical inhibition	Reduced self-administration Prevented drug- and cue-induced reinstatement of self-adminstration
Seif *et al.*[39]	Alcohol	Anterior insula input to nucleus accumbens	Optogenetic inhibition	Disruption of alcohol intake when paired with aversive consequence Sparing of alcohol intake in the absence of aversive consequence

insula lesions disrupt drug-related motivation, they appear to spare food-related motivation.

The study by Seif *et al.*[39] deserves particular attention because it provided a highly detailed anatomical, physiological, and behavioral characterization of the role of the insula in specific forms of addictive behavior. In an earlier review,[40] we proposed that the insula, through its inputs into the nucleus accumbens, plays a role in motivating drug seeking in the face of aversive consequences. Seif *et al.* tested this hypothesis directly using a rodent model of aversion-resistant alcohol intake. In their experiments, they trained rats to self-administer alcohol. They then gave some of the rats access to alcohol that was adulterated with quinine (the taste of which is aversive), and the rest of the rats access to quinine-free alcohol. Normally, rats given quinine-adulterated alcohol will drink as much as rats given quinine-free alcohol, indicating resistance of alcohol intake to pairing with aversive consequences. Seif *et al.* then used optogenetic techniques to selectively inhibit excitatory inputs into the nucleus accumbens core from either the anterior insula or the ventromedial prefrontal cortex. Both of these manipulations resulted in a reduction of drinking from quinine-adulterated alcohol, while sparing drinking from the quinine-free alcohol. Furthermore, these manipulations did not alter responding for sucrose when it was paired with quinine, indicating a selective effect on alcohol consumption. Similar results were obtained when alcohol consumption was paired with foot shock. They then performed further electrophysiological and pharmacologic experiments to show that excitatory inputs into the

nucleus accumbens core from both the anterior insula and the medial prefrontal cortex were mediated by hyperpolarization-active *N*-methyl-D-aspartate (NMDA) receptors, that these receptors were upregulated by alcohol intake, and that aversion-resistant alcohol intake could be blocked by infusion of an NMDA receptor antagonist into the nucleus accumbens core. These findings provided clear evidence that the anterior insula's inputs into the nucleus accumbens play a specific role in motivating drug seeking in the presence of negative consequences.

The insula as a locus for interoceptive representation in addiction

Interoception is defined as a set of sensory processes that signal the physiological state of peripheral tissues, including temperature, tissue damage (nociception), itch, pH, chemosensation, and cytokine milieu, as well as taste, ingestive oral sensations, and general visceral sensations arising in the gut, cardiovascular system, and solid organs. According to Craig,[41,42] interoceptive signals have special relevance for homeostasis, and reach the central nervous system (CNS) through a dedicated set of peripheral pathways that converge on the insula. Interoceptive signals first reach the posterior insula bilaterally, which is considered the primary interoceptive cortex where low-level sensory features are processed. This information is then passed to the anterior insula, where higher-order interoceptive representations reach awareness (Fig. 1). The right anterior insula plays a special role in integrating interoceptive awareness into conscious emotional feelings, as well as in a variety of motivational, executive, social, and self-aware processes. The anterior insula sends projections to the basolateral amygdala (BLA),[43] the nucleus accumbens (NAcc),[44] the entorhinal cortex/hippocampal formation,[45] the ACC,[45] and the OFC,[46] which together are likely to mediate these affective, motivational, social, and executive functions. Although the insula appears to play a central role in conscious interoception and emotional feelings, recent evidence from lesion studies suggest that these functions may persist in some form even after extensive insula damage.[47–49]

Interoception plays a critical role in positive hedonic emotions, specifically, the subjective pleasure that is derived from obtaining homeostatic goals. For example, taste is an interoceptive sensation that signals the obtaining of nutrition; without taste there would be few hedonic feelings of pleasure from eating. The evidence for the role of the insula and related systems in sensory and hedonic aspects of taste is extensive, and has been reviewed elsewhere.[50] The insula is also activated by genital sensations[51] and by nongenital sensual touch,[52,53] which signal copulation and social affiliation, respectively. In addition to its role in representing interoceptive stimuli that impinge directly upon the body, the insula also plays roles in a variety of emotional, motivational, and social processes that involve the anticipation or mentalization of interoceptive states. For example, the right anterior insula is activated during empathy for pain in a loved one, whereas the posterior insula is activated by the direct experience of pain.[54] Similarly, the right anterior insula is activated by the anticipation of sensual touch, whereas the posterior insula is activated by the touch itself.[55] The anterior insula of monkeys contains neurons that respond to sweet tastes, as well as neurons that respond during the anticipation of sweet tastes, with the dynamics of neural activity predicting the timing of taste delivery.[56] Together, these findings suggest that, whereas the posterior insula represents interoceptive stimuli during hedonic experience, the anterior insula, in particular the right anterior insula, is involved in recalling these representations from memory and holding them in mind while simulating the hedonic experience of the self or of others.

Nearly all drugs of abuse exert interoceptive effects. Importantly, we use the term interoceptive to refer specifically to discriminable drug effects that are localized in the periphery, which is different from the historical use of the term in the addiction literature to mean any discriminable drug effect, without regard to its anatomical locus. Smoking tobacco, drinking alcohol, and intranasal cocaine or heroin use are all drug-taking rituals that stimulate chemosensory afferents within the oropharyngeal and nasal mucosa, including taste receptors. Cocaine, amphetamines, nicotine, opioids, and alcohol all exert powerful effects on the autonomic nervous system. These are all interoceptive effects, by virtue of the specific sensory receptors and peripheral afferent pathways that relay the sensations to the brain. They are highly distinctive for each drug of abuse, because each drug stimulates a different set of peripheral receptors. Interoceptive effects are notably different from direct CNS drug effects (i.e., dopamine release) which are less useful for

discriminating between different drugs, or between drugs and other rewards.

Interoceptive drug effects are important sources of pleasure and reinforcement from drug use. Rose *et al.* have shown in a large number of studies that the chemosensory effects of tobacco smoke are a primary determinant of the pleasure and satisfaction that are derived from smoking.[57] We have shown that the airway sensory effects of nicotine are an important component of the reward from individual puffs from cigarettes.[58,59] All of this is well known to the tobacco industry, which has enhanced chemosensory effects to maximize market share.[60] The role of interoceptive effects in cocaine reinforcement was demonstrated by Wise *et al.*,[61] who showed that a cocaine analogue that stimulates peripheral effects but does not cross the blood–brain barrier reinstates cocaine-seeking behavior in rats, and also elicits glutamate release in the ventral tegmental area. They further found that these effects occur only in cocaine-experienced animals and not in cocaine-naive animals, which suggests an important role for learning. The role of learning is further evident in the fact that the interoceptive effects of smoking, which are such an integral part of smoking pleasure and satisfaction, are almost always aversive in first-time smokers. Such learning, along with the neural plasticity that underlies it, may serve as a hedonic switch from casual use to addiction, from finding the interoceptive drug effects aversive to finding them pleasurable, desirable, and needed.

A number of studies provide support for the role of the insula in representing interoceptive drug effects. We have found that left insula damage disrupts the ability of addicted smokers to discriminate the airway sensory effects of nicotine.[40] Albrecht *et al.*[62] found that the chemosensory effects of nicotine in the nasal mucosa activate the anterior insula and posterior insula bilaterally in nonaddicted smokers. Filbey *et al.*[63] found that the taste of alcohol activates the insula in heavy drinkers. In a related study,[64] the same group found that heavy drinkers with longer variants of the DRD4 dopamine receptor have greater activity in the right insula to the taste of alcohol, compared to those with shorter variants. Castro[65] showed that inactivation of the posterior insula in rodents disrupts the ability to discriminate alcohol's chemosensory effects. There is also evidence that addiction is associated with alterations in the processing of nondrug interoceptive stimuli by the insula. For example, Paulus *et al.*[66] showed that methamphetamine-addicted individuals have attenuated responses to sensual touch in the insula bilaterally. More research is needed to characterize the nature of the drug- and nondrug–interoceptive representations within the insula in addicted individuals, how they are translated into hedonic drug experiences, how they are encoded into and recalled from memory, their interaction with direct CNS drug effects, and how they contribute to addictive behavior.

The insula as a control system in addiction

The insula has been implicated in a number of executive-function and impulse-control processes that involve weighing the pursuit of certain rewards against uncertain negative consequences, that is, decision making under risk. Damasio[16] initially proposed that the anterior insula is part of a network of brain areas that guides decision making under risk and uncertainty by marking various options for behavior in terms of their potential negative consequences. According to Damasio, this marking function is accomplished through the deployment of somatic states that derive from the somatic consequences of prior decision outcomes, which are subsequently represented by the anterior insula when these outcomes are contemplated during the selection of various choices for behavior.

Subsequent work has provided strong support for the role of the insula in decision making under risk. Kuhnen and Knutson[67] have shown that activity in the left anterior insula during a financial decision-making task increases before mistakes where subjects do not take risks when they should to maximize gain. Preuschoff *et al.*[68] have shown that bilateral activity in the anterior insula correlates with errors in risk prediction, indicating that the insula may play a role in updating risk representations. Xue *et al.*[69] showed that bilateral activity in the anterior insula during decision making correlates with subsequent risk taking. A more recent paper[70] showed that activation in the right insula was linearly related to the magnitude of potential loss and probability of loss (i.e., risk). Mohr *et al.*[71] performed a meta-analysis of functional-imaging studies of reward-based decision making and found that the insula consistently represented the riskiness of decisions involving potential losses. These functional-imaging

findings have been corroborated in studies where insula functions have been disrupted. For example, Clark *et al.*[72] showed in humans that lesions of the insula disrupted the ability to use information about the probability of losses to update decision-making strategies in a gambling task. Ishii *et al.*[73] showed in rodents that inactivating the anterior insula reduced risk preference.

Menon and Uddin[74] proposed a model in which the anterior insula provides a bottom-up signal to the ACC that a salient event such as a negative consequence has occurred. A related model is one in which the insula, along with the ACC, plays a role in error awareness,[75] because errors are a kind of salient event. According to these models, the ACC–anterior insula system, through its connections to prefrontal regions, switches the brain from a default mode primarily involving the ventromedial prefrontal cortex and the posterior cingulate cortex to an executive mode involving the dorsolateral and posterior parietal cortex. This model is consistent with the anatomical connectivity between the anterior insula and the ACC,[45] the functional connectivity between the dorsal ACC and the orbital frontoinsular cortices of the salience network,[76] as well as the existence of a form of highly specialized Von Economo neurons that only are found in the anterior insula and the ACC in higher primates.[77] A key prediction of the Menon *et al.* model is that information flows directionally from the anterior insula to the ACC during task switching, which has been shown indirectly by Granger causality analysis of functional magnetic resonance imaging data.[78] This model would need to be reconciled with models in which the anterior insula plays a role in executive processes that occur subsequent to the detection of salient events, such as prediction of future risk and reward.

A number of studies have suggested that abnormalities in insula function during executive and impulse-control processes play a role in promoting addiction. Bechara *et al.* have postulated that abnormalities in somatic marker representation by the insula during risky decisions is a core deficit that underlies continued drug use in the face of negative consequences.[79] Paulus *et al.*[66] showed that stimulant abusers had a reduced tendency to shift decisions away from losing responses during a decision-making task, and that individual differences in the tendency to make these loss-related behavioral shifts were inversely correlated with left insula activity. In an earlier study,[80] Paulus *et al.* showed that activity in the right insula during a similar decision-making task in abstinent methamphetamine abusers predicted continued abstinence at 1 year. Villafuerte *et al.*[81] showed that, among individuals who had a family history of an alcohol-use disorder, those who carried a higher-risk allele of the *GABRA2* gene had increased right insula activity during a monetary incentive delay task. Claus *et al.*[82] found that differences in left anterior insula activity between choosing larger, delayed rewards and smaller, immediate rewards correlated with alcohol use–disorder severity. Devito *et al.*[83] showed that activity in the left anterior insula in individuals with a family history of alcoholism was increased during successful inhibitions in a go/no-go task and that this activity correlated with alcohol-use measures. Together, these findings suggest that the insula plays a role in two potentially related processes that may be perturbed in addicted individuals and that may contribute to an impaired ability to control drug seeking in the face of negative consequences: (1) a magnification of incentive representations, especially of short-term rewards, and (2) a discounting of risk representations. These deficits may contribute to difficulties controlling drug-seeking behavior when there are negative consequences or when there are competing long-term rewards.

Such perturbations in executive and impulse-control processes may reflect a loss of function within the insula. As such, they may be related to structural and resting functional abnormalities in the insula that are correlated with addiction severity. For example, cocaine-dependent individuals have reduced gray matter density in the anterior insula bilaterally compared to controls.[84,85] Furthermore, reductions in right anterior insula gray matter volume in cocaine addiction are correlated with impulsivity involving a lack of premeditation.[86] Methamphetamine-dependent subjects have smaller volume of the left insula than controls.[87] Heroin-dependent individuals have lower gray matter volume in the right posterior insula compared to controls.[88] Detoxified alcoholics have reductions in left posterior insula gray matter volume,[89] as well as reductions in anterior insula volume bilaterally that are positively correlated with years of drinking and inversely correlated with duration of abstinence,[90] suggesting that alcohol

exposure causes structural abnormalities in the insula. Dependent smokers have higher gray matter density in the left anterior insula compared to nonsmokers.[91] There is some inconsistency with respect to addiction being associated with increased versus decreased gray matter volume/density in the insula, which may be due to methodological differences between studies or to differential effects of specific drugs. A number of functional-imaging studies across different drugs of abuse have identified abnormalities in insula resting-state connectivity with subcortical and prefrontal cortical networks.[92–94] These structural and resting functional abnormalities within the insula may represent an increased vulnerability to addiction owing to genetic or developmental factors that precede the onset of drug use, or they may result from the neurotoxic effects of repeated drug exposure.

An integrative model of the role of the insula in addiction

How is it that the insula can play a role in both motivational processes that drive ongoing drug use and relapse, such as craving, as well as executive functioning/inhibitory control processes that rein in drug use in the face of negative consequences? Furthermore, what role, if any, do the interoceptive functions of the insula play in craving, relapse, and decision making about drug use? Here, we attempt to answer these questions within an integrated theoretical framework for the role of the insula in addiction. We have discussed elements of this framework elsewhere,[14,40] and here we build upon our earlier model, providing an evolutionary context and integrating more recent findings on the role of the insula in goal-directed behavior.

We propose that the central function of the insula in addiction is to represent the interoceptive effects of drug taking in the service of goal-directed drug seeking. Drug taking is the outcome, or goal, of drug-seeking behavior. Drug taking satisfies a homeostatic function in addicted individuals.[4,95] As with other homeostatic goals (e.g., eating, copulation, and social attachment) drug taking exerts highly salient interoceptive effects that produce immediate feelings of pleasure, gratification, and satiety and signal that homeostasis has been obtained. Interoceptive drug effects, by virtue of being rapidly transmitted to the CNS through sensory channels that have evolved to signal attainment of homeostatic goals, come to signal, through a learning process, the attainment of drug-taking goals.

The human brain has evolved to associate the attainment of homeostatic goals with specific actions that lead to their occurrence (action–outcome association), to increase the likelihood of their attainment in the future. Interoceptive information allows access to representations of the hedonic value of specific outcomes during goal-directed behavior that involves weighing multiple possibilities for action.[96] Interoceptive information is discriminable, that is, it allows for internal representations that differentiate between rewarding outcomes of varying homeostatic significance. Thus, interoceptive drug effects are used to access information about the value of drug-taking outcomes during drug seeking and to allow for internal representations of drug taking that differentiate this goal from other potential goals. Such goal-representation functions are poorly served by direct CNS drug effects such as the facilitation of dopamine release, which by itself does not differentiate between drug taking and other rewards.

During human evolution, seeking of rewards usually occurred in the context of uncertain negative consequences (i.e., risk) or at the expense of competing rewards. For example, seeking food required foraging and hunting, which exposed the organism to potential predation. During times of starvation, seeking food would have taken priority over other pleasurable homeostatic goals, such as copulation. Similarly, drug taking may result in uncertain negative consequences (e.g., illness, arrest, conflict with significant others) or may occur at the expense of competing rewards that may appear more or less homeostatically relevant (e.g., work, relationships, money). Thus, as with the seeking of natural rewards, drug seeking requires the addicted individual to overcome an innate aversion to risk and to disengage with other, less apparently valuable rewards. This is a decision-making process that takes into account the predictive value of drug taking, the probability and magnitude of negative consequences (i.e., risk), as well as the predictive value of competing rewards. In addition, it requires a motivational signal that energizes drug seeking, along with selective attention that is focused on drug taking and not on other goals.

In the absence of apparent risk or competing goals of greater value, drug seeking occurs automatically. This is especially the case in addicted individuals, as

outlined in Tiffany's cognitive model of addiction.[97] Clinically, this is seen when addicted individuals take drugs absentmindedly without feeling a conscious desire to take drugs, or without a memory for what triggered their drug taking. In this model, subjective craving is triggered only when there is an impediment to drug use, which can include negative consequences or the presence of alternative rewards. Thus, craving can be conceptualized as the subjective experience of drug seeking in the face of conflict.

A number of authors[2,98] have postulated a distinction between automatic reward seeking and goal-directed reward seeking. Automatic reward seeking is highly stimulus driven and occurs through simple stimulus–response associations that are divorced from the hedonic value of specific outcomes. According to Robbins and Everitt,[2] the neural substrates for automatic reward seeking include the central nucleus of the amygdala, the dorsal striatum, and the substantia nigra pars compacta, which together function to detect reward-related stimuli and initiate and sustain reward-seeking behaviors, even when the outcomes of these behaviors are no longer homeostatically valuable. In contrast, goal-directed reward seeking involves the explicit representation of contingencies between actions and the hedonic value of their outcomes. Goal-directed reward seeking is evident, for example, when behaviors directed at specific rewards are reduced when their outcomes are devalued, while behaviors directed at other, nondevalued rewards are unchanged. Goal-directed reward seeking, also known as instrumental action–outcome contingency learning, depends upon several integrated functions: (1) the ability to form associations between cues and the primary hedonic value of the specific rewards that they predict, mediated by the BLA;[99,100] (2) the ability to predict the hedonic value of future rewards, mediated by the ventromedial prefrontal cortex;[101,102] and (3) the ability to integrate predictive reward representations with reward-seeking motor programs to initiate and sustain goal-directed actions, mediated by the nucleus accumbens and its dopaminergic innervation from the ventral tegmental area.[103,104] In addition, goal-directed reward seeking, like all forms of goal-directed behavior, requires (4) working memory and attentional functions that hold goal representations online, mediated by the dorsolateral prefrontal cortex,[105] as well as (5) monitoring conflict between reward seeking and competing goals that may require a shift in behavioral set, mediated by the dorsal ACC.[106] The insula plays an important, though less studied, role in goal-directed reward seeking. Specifically, the insula is critically involved in using information about the sensory impact of specific rewards to retrieve their hedonic value from memory.[107] This is consistent with evidence reviewed above that the anterior insula holds interoceptive representations of predicted homeostatic rewards over delays, and suggests that the insula may function to retrieve these interoceptive representations from memory and hold them in mind during the planning of goal-directed behavior. This may occur through connections between the insula and the ventromedial prefrontal cortex, the BLA, the dorsolateral prefrontal cortex, and the ACC, as reviewed above.

Thus, the insula, in particular the anterior insula, may play a specific role in goal-directed drug seeking, that is, a mode of drug seeking that is brought online when there is a conflict between drug taking and alternative goals (e.g., avoiding negative consequences, obtaining alternative rewards) and which is tied to explicit representations of the hedonic value of drug taking. Furthermore, the insula links the action of drug seeking to the value of drug taking through specific, discriminative interoceptive representations of drug taking. This occurs through a convergence of inputs from the anterior insula, amygdala, and the ventromedial prefrontal cortex onto the nucleus accumbens.[39,108,109] According to our model, this leads to a coherent goal representation of drug seeking, which integrates exteroceptive features (e.g., the people, places, and things that are associated with drug taking), interoceptive features (e.g., the taste of alcohol, the feeling of tobacco smoke in the back of the throat), and a specific value (i.e., a higher value of the drug-taking goal under conditions of withdrawal or stress). This coherent goal representation supports a highly targeted form of goal striving that remains on track because of the specificity of the interoceptive representations of drug taking. The conscious feeling of cue-induced craving is the subjective manifestation of the goal-striving process, and is phenomenally derived from embodied memories for interoceptive drug effects, along with subjective urgency and goal frustration.

According to this model, the insula does not play a role in automatic drug seeking, which is

mediated by the central amygdala–dorsal striatal system. Rather, the insula is brought online with the rest of the goal-directed system when normally automatic drug seeking is interrupted by a negative consequence or by the availability of an alternative homeostatic goal with higher motivational salience. This occurs when the ACC detects conflict between ongoing drug-seeking behavior and negative consequences or alternative goals, and brings the insula–vmPFC–nucleus accumbens system online to overcome these impediments to drug taking. This ensures that the organism is able to maintain striving toward drug-taking goals, even in the face of hurdles posed by alternative goals and negative consequences. This system evolved to promote survival by motivating the attainment of natural homeostatic goals (food, sex, hydration) in the face of scarcity, competition with conspecifics, and predation. It is co-opted by drug-seeking and drug-taking behavior in addicted individuals, and comes to motivate drug-taking goals in the face of social, occupational, medical, financial, and legal consequences.

The goal-directed mode of drug seeking predominates when drug users are experimenting with drugs, before becoming addicted. At this stage, drug seeking is driven primarily by a desire to obtain positive hedonic effects, and it is relatively easily to rein in because it is under control of a system that weighs the seeking of pleasure against its negative consequences and against other, more adaptive pleasures. Over time, with repeated use of the drug, drug seeking shifts from the goal-directed mode to the automatic mode, largely as a result of dopamine-induced neural plasticity.[2] As a result, drug seeking becomes increasingly more difficult to stop, even as negative consequences accumulate. Although the automatic system predominates in the day-to-day drug seeking of an addicted individual, the goal-directed system plays an important role in sustaining addiction in the face of hurdles, such as running out of money to buy drugs or social pressures to reduce drug use. These are situations where craving is often experienced, and where decisions are made that maximize the likelihood of drug use in the face of these hurdles.

According to this model, insula lesions should only have an effect on goal-directed drug seeking, not automatic drug seeking. Specifically, insula lesions decouple interoceptive drug effects from their predicted (imagined) value, and thereby abolish goal-directed drug seeking and the associated subjective experience of craving. In our initial study[11] we found no significant effect of insula lesions on the rate of quitting smoking, but among those who did actually quit after lesion onset we found large effects on the likelihood of quitting easily, immediately, without relapsing, and without cravings. This may be because insula lesions have a larger effect on smokers who are motivated to quit due to experiencing a negative consequence (e.g., having a stroke); the insula lesion itself does not alter the automatic tendency to smoke, which is not interrupted in the smokers who do not quit after a stroke. Similarly, this may explain why Bienkwoski *et al.*[20] did not find effects of insula lesions. Their study was completed in Poland, where prevailing attitudes toward smoking are more permissive than in the United States and where having a stroke may not have the same motivational impact on quitting as it does for American smokers. Most convincingly, this model is supported by the findings of Seif *et al.*,[39] who showed that blocking insula inputs into the nucleus accumbens only affected alcohol self-administration when it was paired with a negative consequence (bitter taste, foot shock). They also found the same effects for blocking vmPFC inputs into the nucleus accumbens, which provides strong support for the broader network model for goal-directed drug seeking that we have proposed (Fig. 3).

Alternative models

The model we have presented emphasizes a role for the insula in encoding and recalling interoceptive drug effects to help motivate and focus goal-directed drug-seeking behavior. This is essentially a gain-of-function model, where insula functions that have evolved to promote the attainment of homeostatic rewards are co-opted by drugs and drug-related stimuli. Alternatively, the insula may undergo a loss of function in addiction, especially functions related to risk representation and saliency detection. This would reduce the ability to use information about negative consequences to shape or modify drug-seeking behaviors. This would be similar to the role of dysfunction in the ventromedial prefrontal cortex in addiction, as described by Bechara.[5] Clinically, such deficits in insula function would manifest as an inability to shift away from drug seeking in the face of negative consequences, or as a lack of insight.[110] Such deficits would also promote a number of psychosocial problems that tend to co-occur

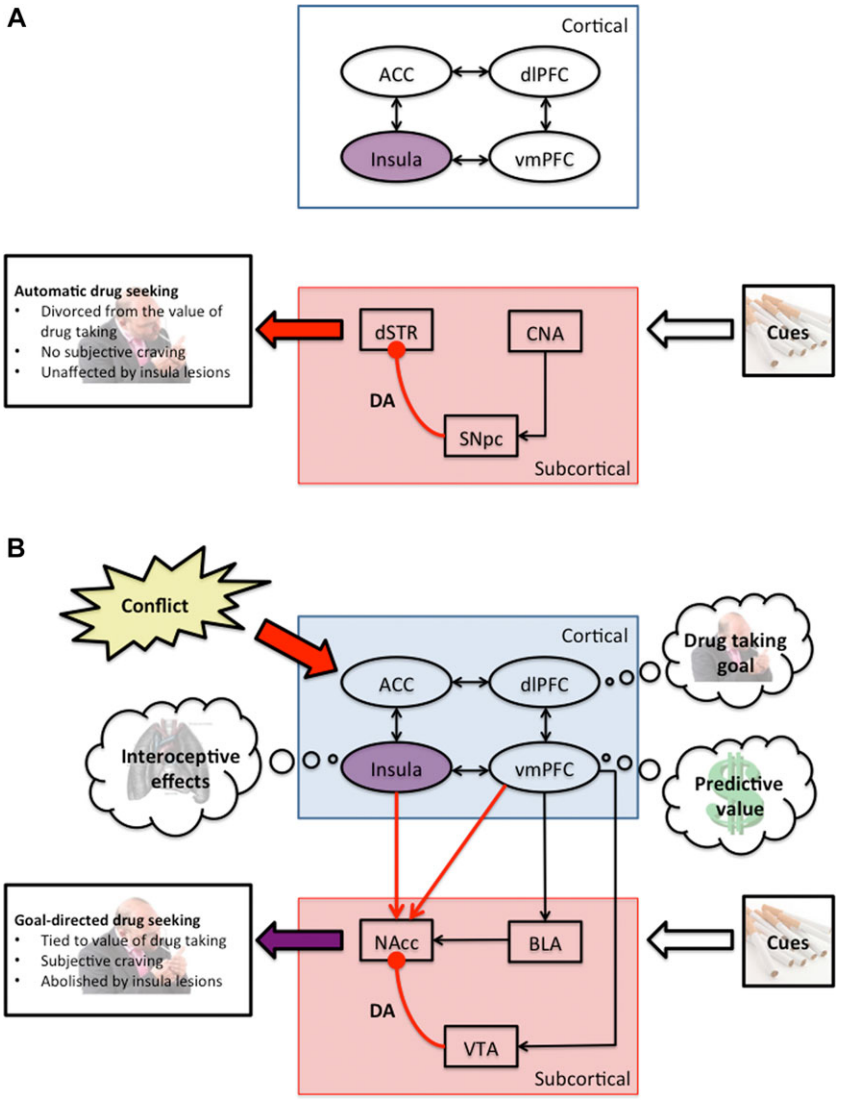

Figure 3. A model for the insula's role in addiction. (A) Without the presence of conflict, drug seeking proceeds automatically, that is, it is divorced from the value of drug taking and it is not subjectively experienced as craving. Automatic drug seeking is largely stimulus (cue) driven. The stimulus–response process is mediated by subcortical systems, including the central nucleus of the amygdala (CNA) and its outputs to the dopaminergic systems in the substantia nigra pars compacta, which innervate the dorsal striatum (dSTR) and thereby initiate habits and automatic cognitive processes. Automatic drug seeking does not engage cortical systems for goal-directed behavior. As a result, it is not affected by insula lesions. (B) The cortical network for goal-directed drug seeking is brought online by the anterior cingulate cortex (ACC), which detects conflict between drug taking and other goals. The insula holds representations of interoceptive drug effects in mind and allows access to the current value of drug taking, which is represented in the ventromedial prefrontal cortex (vmPFC). The dorsolateral prefrontal cortex (dlPFC) coordinates working memory and attentional functions that are necessary for this integrated goal representation. The output of the cortical goal-directed system is directed through the nucleus accumbens (NAcc), which links integrated goal representations with motivational signals provided by the basloateral amygdala (BLA) and dopamine (DA) release from the ventral tegmental area (VTA). The resulting behavior is goal directed (i.e., it is tied to the value of drug taking), as well as subjectively experienced as craving. Insula lesions decouple drug taking from its predictive (imagined) value, and thereby abolish goal-directed drug seeking and its associated experience of craving.

with addiction, such as sexual risk taking, criminality, and violence. A model that integrates both gain and loss of function within the insula is one in which the insula is hyperresponsive to drugs and related stimuli, which serve to stimulate the ventral striatum and other downstream reward-related regions to magnify the incentive representations of drugs and related stimuli. This, in turn, may reduce the perceived magnitude of negative consequences, disrupting the ability of prefrontal regions to use this information to process risk. Further research is needed to clarify whether insula representations of drugs and related cues can modify risk processing in the prefrontal cortex.

Paulus *et al.* have proposed a model of abnormal alliesthesia for interoceptive rewards in addicted individuals. In their model, repeated drug use places the body into a state of perturbed homeostasis that is experienced as aversive, reflected, for example, in the tendency to undergo drug withdrawal. At the same time, drug cues become conditioned stimuli that predict a return of the body state to homeostasis, and therefore come to be desired and pursued. Upon exposure to drug cues in the absence of drug taking, a body prediction–error signal is generated by the insula, which corresponds to the discrepancy between the current dyshomeostatic body state and a predicted homeostatic body state. This error is signaled to downstream regions involved in motivated behavior, such as the ventral striatum, to engender drug seeking and the subjective experience of craving. This model shares with our model a role for the insula in generating signals based on interoceptive drug effects that motivate behavior. It differs substantially in focusing primarily on relief from aversive interoceptive drug effects, namely dyshomeostatic body states such as withdrawal that are experienced as negative affect (e.g., anxiety, irritability), as the goal of drug-seeking behavior. This model has considerable similarity to conditioned withdrawal/negative reinforcement models of cue-induced craving[111,112] as well as neurobiological models that conceptualize addiction as an allostatic reward-dysregulation process.[4]

Clinical implications

The most obvious clinical implication of our findings on the effects of insula damage on quitting smoking, and of subsequent studies confirming the insula's role in incentive motivational processes that drive addiction, is that inhibiting the function of the insula should be an effective treatment for addiction. Although surgically lesioning the insula is neither practical nor safe, there are less invasive techniques that may ultimately prove effective for reducing cravings and drug-seeking behaviors. These include neuromodulation techniques, such as deep brain stimulation and repetitive transcranial magnetic stimulation (rTMS), which have already been shown to alter addictive behavior when targeted at regions such as the nucleus accumbens[113] and the dorsolateral prefrontal cortex.[114,115] Recent improvements in rTMS allow for targeting deeper cortical structures, such as the insula,[116] providing a potentially safe and effective means of modulating insula function. Insula function may also be manipulated pharmacologically, either directly through drugs that bind receptors in the insula, or indirectly through drugs that bind elsewhere but have downstream effects on insula function. For example, in functional-imaging studies it has been shown that partial nicotinic acetylcholine receptor agonists that aid smoking cessation decrease resting-state functional connectivity between the left posterior insula, the vmPFC, and the amygdala in 12-h abstinent smokers,[117] and that baclofen, a $GABA_B$ agonist that has efficacy in a number of substance-use disorders, reduces resting-state activity in the posterior insula bilaterally in nonabstinent cigarette smokers.[118] Animal studies have shown that blockade of hypocretin receptors in the anterior and posterior insula decreases nicotine self-administration in rodents.[36]

According to the integrative model we have proposed, therapeutic manipulations that target the functioning of the insula should help to reduce drug-seeking behavior and craving when the addicted patient is in a goal-directed drug-seeking state, and not when he/she is in the automatic state. Thus, the insula should play a particularly important role in treatment-seeking individuals, who have interrupted their automatic drug-seeking routine, often as a result of encountering a significant negative consequence or because they wish to improve their chances of achieving more adaptive goals, such as steady work or more satisfying relationships. Once the patient is in treatment, a number of psychosocial interventions may help to further promote and maintain the goal-directed state. For example,

motivational interviewing engages awareness of negative consequences and increases discrepancy between drug use and other, more adaptive goals.[119] Cognitive behavioral coping skills therapy helps individuals become aware of the antecedents and consequences of drug use and maximize the value of adaptive rewards, such as social relationships.[120] Similarly, self-help peer groups such as Alcoholics Anonymous (AA) involve taking a "fearless inventory" of the various negative consequences of addiction, as well as providing a ready-made social system (the AA fellowship) and spiritual engagement that both serve as powerful adaptive rewards. The drug disulfiram produces a highly aversive bodily state when it is combined with alcohol, providing a powerful negative consequence for drinking (though not strictly a psychosocial intervention, disulfiram's effects are produced through a psychological representation of a severe negative consequence). By promoting awareness/saliency of negative consequences, increasing the value of alternative rewards, and reducing automaticity, all of these psychosocial interventions engender the goal-directed state, thereby rendering addicted individuals more susceptible to biological interventions targeted at the insula.

Within this neurocognitive framework, psychosocial treatments, which promote the goal-directed state, can work synergistically with biologically oriented treatments that specifically modulate the functioning of the insula. This is different from therapeutic approaches that seek to simply knock out brain regions that drive addictive behaviors or to remediate the functioning of brain regions that govern self-control. It takes into account the complex, state-specific functions of the insula in addiction, addressing processes that are tied to representation of goals, appreciation of risks, ambivalence, and subjective feelings—all of which are particularly human aspects of addiction. Furthermore, this model moves the notion of treatment from one in which medications act on the brain and psychosocial interventions act on the mind to one where all behavior change, whether it is promoted by life circumstances, a medication, or a psychosocial treatment, is rooted in specific neural and cognitive functions that interact in lawful ways.

Conflicts of interest

The authors declare no conflicts of interest.

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