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Interoception and Drug Addiction

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Abstract

The role of interoception and its neural basis with relevance to drug addiction is reviewed. Interoception consists of the receiving, processing, and integrating body-relevant signals with external stimuli to affect ongoing motivated behavior. The insular cortex is the central nervous system hub to process and integrate these signals. Interoception is an important component of several addiction relevant constructs including arousal, attention, stress, reward, and conditioning. Imaging studies with drug-addicted individuals show that the insular cortex is hypo-active during cognitive control processes but hyperactive during cue reactivity and drug-specific, reward-related processes. It is proposed that interoception contributes to drug addiction by incorporating an “embodied” experience of drug uses together with the individual’s predicted versus actual internal state to modulate approach or avoidance behavior, i.e. whether to take or not to take drugs. This opens the possibility of two types of interventions. First, one may be able to modulate the embodied experience by enhancing insula reactivity where necessary, e.g. when engaging in drug seeking behavior, or attenuating insula when exposed to drug-relevant cues. Second, one may be able to reduce the urge to act by increasing the frontal control network, i.e. inhibiting the urge to use by employing cognitive training.

Keywords

Interoception; insula; embodiment; relapse; cue reactivity

1. Interoception, homeostasis, and drug-taking behavior

Interoception (Craig, 2002, 2009), i.e. receiving, processing, and integrating body-relevant signals with external stimuli to affect ongoing motivated behavior, is an important process that contributes to the degree to which individuals approach or avoid drugs of abuse. Interoception can be viewed as a state of the individual, i.e. the way a person “feels” at a particular point in time (Craig, 2010), or it can be viewed as sensing body-related information in terms of awareness (Pollatos et al., 2005), sensitivity (Holzl et al., 1996), or accuracy of the sensing process (Vaitl, 1996). Interoception is thought to serve a homeostatic function (Craig, 2003) such that an individual’s approach or avoidance behavior toward stimuli and resources in the outside world is aimed at maintaining an equilibrium.

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For example, a person will approach a heat source in a cold environment but avoid it when the ambient temperature is high. Interoception provides an anatomical framework for identifying pathways that are focused on the modulating the internal state of the individual. This framework comprises peripheral receptors (Vaitl, 1996), c-fiber afferents, spino-thalamic projections, specific thalamic nuclei, posterior and anterior insula as the limbic sensory cortex and the anterior cingulate as the limbic motor cortex (for reviews see (Augustine, 1996; Craig, 2007)). Whether viewed as an integral individual state of “feeling” or as specific sensing of body-related afferents, interoception has profound effects on other brain processes such as cognitive control, emotion, decision-making, reward, stress, and conditioning.

Since the central component of interoception is the body-relevant feeling state, one way to conceptualize the contribution of interoception to these processes is to consider the notion of embodiment (Niedenthal, 2007) of an experience. The basic notion of embodiment theories is that higher-level cognitive and affective processing is grounded in the organism’s sensory and motor experiences (Winkielman et al., 2009). For example, the individual’s original neural state when information was initially acquired is reinstated when a stimulus, an option in a decision-making context, or the reception of a reward is processed. As a consequence, the experience of an emotional state, e.g. anger, is intrinsically linked with the internal body state, e.g. muscle tension. Since the insula cortex is critically important in processing physiological states of an individual, one may view this brain area as an important neural basis for the embodiment of approach or avoidance behaviors.

The homeostatic aspect of interoceptive processing is often overlooked but quite important for approach and avoidance behavior. Specifically, the degree to which a stimulus is approached or avoided is a function of the degree to which the reception of this stimulus brings this individual closer to a homeostatic state. For example, a hungry person will seek out and consume available food but a satiated person may engage in much less food-seeking and consumption behavior. The relationship between a stimulus and the associated degree of approach or avoidance as a function of the internal state of the individual was described as by Cabanac as alliesthesia (Cabanac, 1971). The internal state can enhance approach or avoidance behavior, which has been called positive alliesthesia, or attenuate such motivated action, which refers to negative alliesthesia. There is some evidence that deprivation states such as hunger and thirst enhance the responsiveness of neural systems to internal stimuli (Tataranni et al., 1999). In other words, a hungry individual may experience visceral afferents more intensely than a satiated person (Piech et al., 2009). Internal state dependent changes in approach or avoidance behavior can transcend the specific reward stimulus, e.g. food restriction also confers positive alliesthesia to alcohol preference (Soderpalm and Hansen, 1999). The relationship between deprivation state and intensity of interoceptive processing has important consequences for drug abuse research. For example, the degree to which cognitive control systems influence ongoing behaviors could be a function of the deprivation state and the associated intensity of interoceptive afferents. Specifically, optimal control could be an inverted U-shape function of the interoceptive state. As a result, low levels of “embodied” experience may not engage the cognitive control system to adjust ongoing behavior. In comparison, a highly “embodied” experience may “overwhelm” the cognitive control system by providing a highly emotionalized experience.

One way to conceptualize drug-taking behavior is to pose that individuals take substances to feel better or to avoid feeling worse. The positive and negative reinforcing aspects of drugs of abuse have given rise to a tremendous insight into the behavioral processes (Koob and Le Moal, 1997; Robinson and Berridge, 2003), neural systems (Everitt and Robbins, 2005; London et al., 2000), and molecular mechanisms (Kalivas and Volkow, 2005; Nestler and Aghajanian, 1997) of drug addiction. More recently, there has been an increased realization

that body-relevant information and its associated neural circuits may also play an important role in drug addiction (Naqvi and Bechara, 2010; Naqvi et al., 2007). However, the framework for this approach is much less developed and needs further empirical validation. In particular, the relationship between previously examined constructs important for drug addiction and interoception needs a more detailed evaluation. Thus, in this review we delineate the relationship between interoception and other important behavioral processes with high relevance for drug addiction. Evidence for insula dysfunction is summarized for four substance use populations: nicotine, marijuana, amphetamine, and cocaine dependent individuals. Lastly, we integrate the findings to suggest three important topics of future research that will help to determine the role of interoceptive processing in drug addiction.

2. A brief introduction to the insular cortex: The interoceptive hub

The insular cortex (Augustine, 1985) is a complex brain structure that can be most easily viewed as organized macroscopically along an anterior-posterior (Craig, 2002) and superior-inferior axis (Kurth et al., 2010). This macroscopic organization is partially consistent with the microscopic structure of the insula, which shows granular, dysgranular, and agranular columnar organization from posterior to anterior insula (Chikama et al., 1997; Shipp, 2005). A recent meta-analysis shows that the anterior-posterior subdivision is delineated more clearly on the right side. The anterior cluster is predominately activated by effortful cognitive processing, whereas the posterior is mostly activated by interoception, perception and emotion (Cauda et al., 2012). Moreover, the anterior insula, potentially together with the anterior cingulate cortex, appears to pivotally influence the dynamics between large-scale brain networks subserving both default-mode and executive control network information processing (Sutherland et al., 2012). One has to be careful to engage in extensive inverse inference statements, i.e. the degree to which one ascribes activation in a particular context in a brain structure to a process that involves this brain structure in another context. However, the paucity of studies examining the neural basis of direct interoceptive assessments in individuals with drug addictions compels one to carefully consider the insula involvement in various studies as contributing to the embodied experience.

3. The interface between interoception and basic behavioral processes

Arousal

Arousal, conceptualized as the degree to which an individual reacts physiologically and psychologically to stimuli, involves the activation of the reticular activating system in the brain stem (Moruzzi and Magoun, 1949) as well as the autonomic, endocrine, and limbic systems (Quinkert et al., 2011). Individual differences in levels of arousal have long been thought to contribute to susceptibility to using drugs (Zuckerman, 1974). Specifically, it has been hypothesized that subjects use drugs to adjust to an optimal level of arousal. As pointed out above, visceral afferents are mapped hierarchically in the brain and influence efferent signals. The neural circuits involved in processing these afferents overlap substantially (de Morree et al., 2013) with those involved in arousal-related processing (Critchley, 2009). Thus, interoceptive processing involves components of arousal and this conceptual relationship is supported empirically by a number of different studies. For example, anterior insula showed sustained activity during extended emotional contexts that tracked positively with levels of arousal (Somerville et al., 2012). Monitoring skin conductance as a measure of arousal, the degree of anterior insula activity was correlated with the interaction between accuracy and sensitivity to biofeedback (Critchley et al., 2002). Furthermore, modulation of interoceptive afferents such as rectal distention, which leads to substantial increase in plasma adrenaline and sympathetic arousal as characterized by increased heart rate as well as low versus high frequency heart rate variability, shows among other areas significant insula activation that correlates with indices of sympathetic arousal (Suzuki et al., 2009).

Thus, interoceptive processing, indexed by the sensitivity and accuracy of sensing visceral afferents, may be both affected by and – in turn – affect general levels of arousal. However, it is unclear whether “embodiment” of arousal implies that insula-integrated afferents, which modulate levels of arousal, are necessary or sufficient to change arousal levels, i.e. whether the insula simply acts as a “driver” for different arousal states. Alternatively, one may consider that drug-induced changes act via this route to bring an individual to an optimal level of arousal, i.e. afford the individual access to a particular embodied state to select an optimal response. These are important questions for future research.

Attention

Attention can be conceptualized as the degree to which cognitive resources are allocated to favor processing specific stimuli of the external and internal environment as opposed to others. Attention biases towards drug-related stimuli have been proposed as a key process to maintain drug-taking behavior (Robinson and Berridge, 1993). A different line of research has proposed that attentional dysfunction such as attention deficit hyperactivity disorder is a significant risk factor for future drug use (Biederman et al., 1995). A number of meta-analyses have clearly shown that the dorsal anterior insula is a core component of the executive control network (Cauda et al., 2012; Kurth et al., 2010; Sutherland et al., 2012). Therefore, it should not be surprising that attentional modulation, particularly in the context of interoceptive processing, profoundly affects insula activation. A recent study shows that different regions within the insula orchestrate attention modulated activation of visceral afferents (Simmons et al., 2012b). In particular, activation in the anterior insula is thought to reflect anticipatory affective processing (Simmons et al., 2012a) when individuals expect to experience both pleasant (Lovero et al., 2009) and aversive (Lin et al., 2013) stimuli.

Several studies have used meditation as a means of attentional control of visceral afferents to examine the degree to which attention modulates activation in the insula. For example, experienced meditators show an increased reactivity consisting of low baseline activity coupled with high response in the anterior insula, which was related to accelerated habituation within the amygdala during pain stimulation (Lutz et al., 2012). In addition, these individuals also show greater gray matter concentration in the anterior insula (Holzel et al., 2008), which may be the consequence of attention-related adaptation. Others have shown that degree of mindfulness training was related to more efficient pain processing (Zeidan et al., 2011), greater inhibitory control (Allen et al., 2012), greater interoceptive attention in anterior dysgranular insula as well as altered functional connectivity between posterior insula and dorsomedial prefrontal cortex (Farb et al., 2012). Taken together, training involving attention modulation and interoception increases the efficiency of the insula and associated neural systems when processing afferent information.

There are no studies examining the relationship between attention and interoceptive processing in healthy volunteers or substance use populations. However, animal studies have shown that frequency discrimination of vibrotactile stimulation in the rat under distraction was correlated with activation in – among other areas - the right anterior insula (Soros et al., 2007). Moreover, degree of interoceptive awareness indexed by heartbeat detection accuracy during an exteroceptive task was associated with greater insula and anterior cingulate activation (Pollatos et al., 2007), which may reflect the efferent or motor component of interoceptive processing. The “embodied” aspects of attention processing still need further studies to determine whether different interoceptive states are associated with levels of attention that may make individuals more or less susceptible to initiate drug-taking, drug seeking, or experiencing an increased susceptibility to relapse to using drugs.

Stress

Stress fundamentally involves the individual's response of the hypothalamic-pituitary-adrenal axis during the perception, appraisal, and response to harmful, threatening or perturbing internal or external demands, with the ultimate goal to maintain homeostasis (Selye, 1956). One approach to examine life stress effects is to determine the relationship between cumulative adversity, stress recency and gray matter volume. Smaller volumes of insular cortex have been implicated with increased cumulative adversity and stress recency (Ansell et al., 2012). In a comprehensive review, Sinha has made a compelling case that stress has profound effects on and is influenced by regular and chronic drug use (Sinha, 2008). Specifically, activation during stress-induced and drug cue-induced craving states in the posterior insula appears to be related to an increased susceptibility to relapse (Sinha and Li, 2007). Several studies with substance using individuals have shown an attenuated stress response to experimental stimulations. For example, methamphetamine abusers show reduced insular activation to threatening scenes and empathy for another's pain (Kim et al., 2011a). Interestingly, there appears to be a gender-specific effect of stress in cocaine dependent individuals such that women – as opposed to men – show increased insula activation to stress-related scripts (Potenza et al., 2012). However, in alcohol-related cue exposure men displayed greater stress-related insula activation, whereas women show more cue reactivity in the insula (Seo et al., 2011). Taken together, stress reactivity in the insular cortex appears to be muted in some substance users, possibly in a gender-specific manner, and may provide an index of propensity to relapse.

Reward and Prediction Error

Reward is a complex construct comprised of a feeling and an action. Components of reward include the hedonic aspects, i.e. the degree to which a stimulus is associated with pleasure, and the incentive motivational aspects, i.e. the degree to which a stimulus induces an action towards obtaining it (Berridge and Robinson, 2003). Typically, the feeling is described as “pleasurable” or “positive” and the actions comprise behavior aimed to approach the stimulus that is associated with reward. In a previous review, we have argued that interoception is fundamentally involved in the hedonic and incentive motivational aspects of reward (Paulus, 2007). Recent reward-related neuroimaging studies provide empirical evidence for this proposition. For example, the degree of insula activation appears to code for distributional characteristics of reward delivery (Burke and Tobler, 2011), i.e. given similar expected reward, a high density of low reward possibilities was associated with greater insular activation. In addition, enhancement of the hedonic (Vijayaraghavan et al., 2012) and incentive (Chaudhry et al., 2009) values of an option by both cognitive and affective processes involves the insular cortex. Some investigators have found an exaggerated insula response to monetary reward reception in abstinent cocaine dependent individuals (Jia et al., 2011) and marijuana users (Cousijn et al., 2012) whereas others have found hypoactivity in the left insula cortex in response to loss and loss avoidance outcome notifications in cannabis users (Nestor et al., 2010). In smokers, insula reactivity to reward-related stimuli is highly dependent on the satiation, i.e. the degree to which the individual has recently smoked (Addicott et al., 2012).

The association of dopaminergic signaling (Schultz et al., 1997; Schultz and Dickinson, 2000) as it relates to the differences between expected and obtained reward, i.e. the reward prediction error, is one of the most influential recent developments in understanding reward-related processes. It is well established that activations in the ventral striatum robustly correlate with prediction error (O'Doherty et al., 2003; Pessiglione et al., 2006). In comparison, greater anterior insula activation is associated with an aversive prediction error relative to an appetitive prediction error (Jensen et al., 2007) as well as rewards that are more highly unexpected relative to those that are more expected (Veldhuizen et al., 2011).

Thus, the insula may provide body-relevant information about coding for aversiveness and levels of expectation during reward-related processing. Some have argued that the insula provides a salience signal during reward related processing (Metereau and Dreher, 2013). Taken together, the insula contributes to certain aspects of reward and reward expectation to processing of reward prediction errors. However, it is still an open question whether interoception or “embodied” reward is critical for acquisition of new behaviors or relevant for other learning related phenomena, e.g. extinction or re-instatement. A better understanding of the role of interoception for these processes would provide a compelling argument for modulating interoception as a way of reducing transition from occasional use of drugs to compulsive drug-taking behavior.

Conditioning

The neural processes underlying acquisition and extinction of aversive conditioning are a rapidly emerging area of research in anxiety disorders (Delgado et al., 2011; Milad and Quirk, 2012). Aside from the central role of the amygdala, insular activation have been reported in aversive cue and context conditioning (Marschner et al., 2008), fear acquisition (Reinhardt et al., 2010), fear learning (van Well et al., 2012), conditioned taste aversion (Ma et al., 2011), and potential threat assessment (Fiddick, 2011). A recent meta-analysis found that together with amygdala and anterior cingulate cortex, insular cortex can be considered part of the network underlying fear conditioning (Sehlmeyer et al., 2009). For instance, imaging studies indicate that individual differences during a conditioning procedure were predicted by differential insula cortex responses during videogame conditioning (McCabe et al., 2009) and greater posterior insula thickness resulted in enhanced responsivity during fear conditioning acquisition (Hartley et al., 2011). Moreover, the interaction of the insular cortex with other brain areas such as the red nucleus plays an important role in expectation-modulated fear learning (Linnman et al., 2011). Finally, animal studies support the specific role of ventral anterior insula neurons in the acquisition of an instrumental response during cocaine self-administration (Guillem et al., 2010). In summary, the insula plays a pivotal role in the acquisition and modulation of conditioned aversive responses. Specifically, the role of the insula may be to associate a degree of a visceral response to a previously neutral stimulus to signal hedonic and motivational significance. The role of the insula during aversive conditioning is particularly important considering recent investigations of negative reinforcement mechanisms underlying drug addiction. Taking an aspirin for headaches or leaving home early for work to avoid traffic are daily examples of negative reinforcement. Negative reinforcement is at work when an individual is in or anticipates a negatively valued state and acts to terminate this state. These reinforcers act via brain-related processes in by activating neural substrates of approach or escape responses, producing rewarding or aversive internal states, and modulating information that has been stored in memory. As reviewed by Baker and colleagues (Baker et al., 2004) addicted individuals are thought to take drugs to escape or avoid aversive states such as withdrawal or stress. Baker argues that signs of incipient withdrawal-induced negative affect are detected interoceptively, which subsequently serve as discriminative stimuli for instrumental behaviors. In addition, external stimuli that become associated with such discriminative interoceptive stimuli may function as conditioned stimuli. Therefore, both aversive internal states and conditioned (external) stimuli are important antecedents to non-adaptive behaviors (e.g. compulsive drug use).

Cue reactivity

Within the context of cue reactivity in substance dependence, a conditioned stimulus (CS+) has become associated with significant drug experiences and is therefore linked to increased arousal and attention relative to unconditioned CS- stimuli (CS-). A recent meta-analysis of smoking cue reactivity demonstrates that a network of brain structures including insular cortex is activated during presentation of the CS+ (Engelmann et al., 2012). Furthermore,

CS+ related insula activation is greater in deprived smokers than in non-deprived smokers (Luijten et al., 2010). Finally, smokers with higher degrees of nicotine dependence exhibit higher insula activation during CS+ (Goudriaan et al., 2010). Similar findings are emerging with cocaine dependent individuals (Bonson et al., 2002; Prisciandaro et al., 2013). Others have reported positive correlations between attentional bias and reactivity to smoking images in the insula (Janes et al., 2010). Preliminary evidence suggests that these CS+ related activations undergo extinction during prolonged periods of abstinence, which may signal an attenuated risk of relapse (Lou et al., 2012). Finally, an animal study showing the causal role of the insula in nicotine-induced cue approach behavior (Scott and Hiroi, 2011) further supports the central role of this structure in cue reactivity processing. Presenting a drug-related image to a substance-using individual can be conceptualized as a conditioned stimulus that changes the internal state of the individual towards processing drug-related memories, experiences, and urges to use the drug. Thus, interoception plays a critical part in embodiment of the conditioned response, i.e. “how much the individual feels” and possibly experiences the urge to use, and therefore involves the insula cortex as a key neural substrate. Furthermore, the degree of insular activation may signal severity of dependence and possibly undergo dynamic changes with prolonged sobriety.

4. The role of the insula and interoception in substance use populations

The preceding section showed that interoception is closely linked to a number of processes that have high relevance for substance using populations. However, it was also pointed out that there is relatively little information about the degree to which the “embodied” notion of these constructs is necessary or sufficient to explain the contribution of the insula, or whether dysfunctions in interoception contribute to the disruption of these processes and as a consequence change susceptibility to using drugs. Nevertheless, a number of studies have highlighted the importance of the insular cortex in different target populations. At this time, no published research has investigated interoceptive sensitivity or accuracy in substance using individuals. However, studies of cue reactivity suggest that drug users may show altered interoceptive processing. For instance, Garavan asserts (Garavan, 2010) that drug craving may be an example of the anterior insula’s role in interoception and subjective feeling states, which is influenced by changes in general internal states such as satiety and is influenced by top-down cognitive modulation. For example, there is direct evidence that smoking abstinence state and craving intensity involves a network of brain structures, including the insula (Wang et al., 2007). In comparison, support for insula modulation via top-down control comes from imagery research, which shows that imagery induced cravings in cocaine dependent individuals are associated with insula activation (Kilts et al., 2001)

Nicotine

Several studies have examined insular cortex activation patterns in a variety of experimental paradigms following the important observation that individuals with lesions in this structure lost the “urge” to smoke (Naqvi et al., 2007). Exposure to nicotine-related stimuli increases blood flow in a large network, including the insula cortex (Franklin et al., 2007). In a working memory task, smokers show greater tonic activation in right anterior insula, which was not affected by acute administration of nicotine (Sutherland et al., 2011). Moreover, during reward anticipation abstinent smokers relative to satiated smokers showed greater insula activation (Addicott et al., 2012). Smokers who were more likely to relapse also showed greater insula and anterior cingulate activation to smoking-related images, which correlated with an attentional bias to smoking-related words (Janes et al., 2010). Finally, smokers with higher levels of nicotine dependence showed enhanced insula reactivity to smoking-related pictures (Goudriaan et al., 2010). Therefore, the insula plays a pivotal role in processing smoking related cues, differentially activates as a function of abstinence or

satiation, is related to severity of addiction and may provide a quantitative predictor of relapse.

Cannabis

There are a few studies that have examined the contribution of insula structure and function in individuals with cannabis use disorder. Early studies showed that acute administration of cannabis increased blood flow (O'Leary et al., 2000) as well as functional magnetic resonance imaging (fMRI) perfusion signal (Jacobus et al., 2012; van Hell et al., 2011) in the insula, among other structures. Structural MRI studies have also found reduction of insula cortical thickness in chronic cannabis users (Lopez-Larson et al., 2011). In comparison, several fMRI studies demonstrate that cannabis users exhibit less activation in the insula during inhibitory processing (Hester et al., 2009), which has been linked to reduced error awareness (Nestor et al., 2010). On the other hand, these subjects display an enhanced insular response to cannabis-related cues (Filbey et al., 2009), which seems to attenuate with increasing duration of sobriety (Schweinsburg et al., 2010). Although there have been fewer studies in cannabis users relative to nicotine smokers, a similar pattern of differential insula activation is emerging. The insular cortex is affected by acute administration of cannabis, shows less activation during cognitive control tasks, but enhanced reactivity to marijuana cues. As a whole, these data support the notion that cannabis affects interoceptive regulations.

Amphetamine

In a recent review of the structural MRI data in amphetamine dependent individuals, we concluded that volume reductions in the insula are a common finding across different studies (Mackey and Paulus, 2012), which may represent a reduced ability to appropriately process interoceptive aspects of stimuli that are relevant to goal-directed behavior. Specifically, amphetamine users have both smaller insula gray matter volumes (Nakama et al., 2011) and lower insular gray matter density (Schwartz et al., 2010). However, surprisingly, increases in volume correlated with duration of use, which may point towards a complex interaction between effects of chronic stimulants and insula function (Morales et al., 2012). Positron emission tomography studies examining the dopamine (Sekine et al., 2008), serotonin, and opioid (Colasanti et al., 2012) systems are consistent with an altered response to amphetamines for chronic users in brain structures that include the insula cortex. In addition, fMRI studies show attenuated insula activation in cognitive control (Nestor et al., 2011) and emotion processing tasks (Kim et al., 2011b). This reduced insula response in methamphetamine dependent subjects is contrasted with an enhanced response to pharmacological agents aimed at increasing cognitive control in these individuals using modafinil (Ghahremani et al., 2011). In our studies, attenuated insula activation during a simple decision-making task was associated with increased propensity for relapse (Paulus et al., 2005). Taken together, evidence for smaller insula volumes, altered responsiveness of neurotransmitters in this structure, and functional characteristics of the insula in amphetamine dependent individuals provide a strong argument that interoceptive processing may be affected in this population. Specifically, a reduced sensitivity to internal states, or to afferent signals from the body, which would serve as an "embodied" warning signal, might help to explain why these individuals engage in risky behaviors despite potentially devastating outcomes. However, future investigation will need to examine whether this relates to detection of the internal state, processing of visceral afferents, or the contribution of visceral sensations to conditioned stimuli.

Cocaine

Similar to amphetamine, there are no direct assessments of interoceptive sensitivity or accuracy in cocaine dependent individuals. There is some evidence from structural studies

that cocaine dependent subjects, particularly females, may have smaller insula volumes (Rando et al., 2013). fMRI studies show enhanced insula response in cocaine dependent individuals during monetary reward-related processing (Jia et al., 2011), stress-related imagery (Li et al., 2005), presentation of cocaine-related cues (Bonson et al., 2002), which is related to the degree of craving (Garavan et al., 2000; Kilts et al., 2001). However, in contrast, chronic cocaine users demonstrate attenuated insula activation during an inhibitory task (Kaufman et al., 2003). This reduced insula reactivity in cocaine dependent individuals may undergo dynamic changes as a function of sobriety. For example, relative to individuals with longer periods of abstinence, cocaine dependent subjects with fewer days of sobriety showed greater insula responses during errors on a cognitive control task (Li et al., 2010). Finally, administration of methylphenidate attenuates insula-related brain activation during cocaine-related cues (Volkow et al., 2010). In summary, cocaine dependence is characterized by insular hyperactivity to drug-specific stimuli but hypo-reactivity when engaged in cognitive processes, which may undergo dynamic changes with enhanced sobriety and could be a target for treatment interventions. Nevertheless, a precise understanding of the role of interoceptive processing is still awaiting future research.

Considering the different target populations there is consensus that insula reactivity is reduced during cognitive control tasks but enhanced when individuals are exposed to cues or processes involving reward. These differences are consistent with the notion that cue reactivity involves a significant visceral component and an urge to act to acquire the drug. As pointed out above, cue reactivity can be conceptualized as a conditioned process, which results in association of previously neutral stimuli with strong emotional and incentive motivational properties. Undoubtedly, interoceptive processing by the insula is a key component in this process, which has been pointed out by several investigators (Naqvi and Bechara, 2010; Verdejo-Garcia and Bechara, 2008). This view is consistent with the indirect pathway of the somatic marker hypothesis of emotion (Damasio, 1996) and in line with the general notion of the insula as integrating the emotional experience (Craig, 2002). However, our understanding of the precise role that interoception plays in drug addiction is still far from complete.

5. Drug addiction is more than insula dysfunction

Functional neuroimaging studies using resting state, task-related, and structural connectivity measures have shown that individual brain structures are organized in functional networks (Bellec et al., 2006). Therefore, interoceptive dysfunction in addiction cannot be reduced to simply a dysfunction of the insula. In particular, functional neuroimaging studies have delineated a medial default mode network, a frontal control network, and a limbic salience network (Spreng et al., 2013). Depending on the approach, the insular cortex has been divided into two (Taylor et al., 2008) or three (Deen et al., 2011) compartments, which may serve different functions in these large scale networks. Specifically, the dorso-anterior insula is consistently associated with the frontal control network (Chang et al., 2012), whereas others have suggested that the anterior insula is critical for the saliency network and is functionally connected with frontal, cingulate, parietal, cerebellar brain areas (Sullivan et al., 2013). In comparison, the posterior insula is closely connected to sensorimotor, temporal and posterior cingulate areas (Cauda et al., 2012). Some have proposed that the right fronto-insular cortex together with the anterior cingulate cortex plays a causal role in switching between the frontal control network and the default mode network (Sridharan et al., 2008) and is involved in switching during a variety of perceptual, memory, and problem solving tasks (Tang et al., 2012). Consistent with this notion is the observation that the anterior insula involved in the processing of temporal predictions (Limongi et al., 2013) as well as the influence of self-regulation on functional connectivity (Haller et al., 2013). These connectivity patterns suggest that the anterior insula is important for translating emotional

salience into activation of the cognitive control network to implement goal-directed behavior (Cloutman et al., 2012). Interestingly, the insula has significant downstream influence on the nucleus accumbens and striatum, brain areas that are central for reward-related processing (Cho et al., 2012). Taken together, the insula cortex is likely to be a temporally predictive switching structure to serve large neural networks to engage in motivated behavior. Therefore, it should not be surprising that individuals with drug or alcohol related problems show altered insula functioning as it relates to these large-scale networks. For example, the connectivity between ventromedial prefrontal cortex (Sutherland et al., 2013b) or amygdala (Sutherland et al., 2013a) and insula appears to be altered in smokers, particularly during the withdrawal state (Sutherland et al., 2013b). Specifically, some have reported that smokers show an increased connectivity between insula and the salience network (Claus et al., 2013), whereas others have suggested that the connectivity between the salience network and the default mode network is attenuated in smokers (Ding and Lee, 2013). This may point toward a state-dependent connectivity pattern between the insula and other large-scale networks. Individuals with cocaine dependence show a greater connectivity between insula and the frontal control network (Cisler et al., 2013) and less connectivity to the salience network (Albein-Urios et al., 2013). Finally, altered connectivity between insula and fronto-parietal control network has also been reported in alcoholics during resting state (Sullivan et al., 2013) and inhibitory processing (Courtney et al., 2013). Taken together, altered insula connectivity to the frontal control network and the salience network may represent the altered ability to appropriately modulate goal-directed behavior in accordance with ongoing interoceptive evaluation of the individual's body state. However, more specific studies are needed to link interoceptive processing to the effect of the insula on these large-scale networks.

6. Integration of interoceptive processing dysfunction in drug addiction: Future directions

We have previously conceptualized the degree of motivated approach/avoidance behavior as emerging from a body prediction error (Paulus et al., 2009a; Paulus and Stein, 2006, 2010; Paulus et al., 2009b), i.e. the difference between the experienced and the expected internal state of the individual. However, the simple difference between an experienced and expected body state does not explain opposing insular cortex effects in different task settings in substance use populations. Thus, we have argued more recently that optimal behavior emerges from a computational process involving probabilistic representation of belief states in the context of partially observable Markov decision processes (Paulus and Yu, 2012). In this context, body prediction error is evaluated within the context of the individual's belief about external stimuli and their relevance for specific outcomes. For example, considering a choice of engaging in risky behavior may not appropriately engage the insular cortex to signal the potential aversive outcome. On the other hand, seeing a cue that has previously been associated with drug-taking behavior may generate a large insula response and provide an overwhelming urge to use. This view of the differential contribution of the interoceptive afferents to motivated behavior is consistent with the multi-modal connections of the insula with other brain areas. These modulatory influences may ultimately determine whether an "embodied" state is (a) amplified and experienced, (b) contributes to ongoing behavior, and (c) becomes a target for the cognitive control system to modulate its influence. A similar computational model has been developed by another group (Seth et al., 2011), which proposes that successful suppression by top-down predictions of informative interoceptive signals evoked by autonomic control signals or by visceral responses to afferent sensory signals. The computational framework is particularly useful to consider the acquisition of embodiment by conditioned stimuli and the emergence of conditioned responses. As pointed out by Verdejo-Garcia (Verdejo-Garcia et al., 2012), the relationship between various

“alterations” of interoceptive processing and the development, maintenance, and recurrence of substance use disorder will likely be complex. Specifically, increased liability for substance use may emerge from: (a) a disconnection between the processing of the external stimulus and the attenuated or enhanced embodied experience as a consequence of dysfunctional interoceptive processing, (b) an enhancement of the aversive associations with the cessation of drug use, and/or (c) a re-appraisal of aversive body signals. Furthermore, individual differences in interoceptive processing may provide important insights into different levels of risk for substance use and use disorder. For example, in emotion research, individuals with high interoceptive awareness are likely to engage in reappraisal of emotions, resulting in reduced arousal and more pronounced modulation of underlying neural activity (Fustos et al., 2012). The current conception of the contribution of interoception to drug addiction is based on the idea that the internal state of the individual together with past experiences and predicted body states modulates the degree to which body-relevant information contribute to approach or avoidance behavior, i.e. whether to take or not to take drugs.

The behavioral, physiological, and neuroanatomical framework of interoception enables us to apply a rigorous experimental approach to examine the degree to which individuals at various stages of drug addiction show attenuated thresholds of afferent visceral signals, exhibit aberrant sensitivity to the association of visceral sensations as a consequence of conditioning, or show an altered relationship between top-down modulation and insular integration of the embodied experience. We propose that substances are used to attenuate or enhance the embodied experience to aid in achieving a momentary steady state. For example, stimulants may enhance the experience of an individual who otherwise would not experience strongly embodied pleasure. In contrast, central nervous system depressants may attenuate the embodied experience in an overly aroused individual. With repeated use of these substances conditioning with external stimuli occur that predict the future onset of an embodied experience without the actual emergence of it, creating a deprivation state. This deprivation state in turn initiates motivated behavior to use means to generate the expected embodied experience, i.e. to use the substance again. The critical link between the deprivation experience and the urge to action occurs as the interaction between limbic sensory cortex, the insula, and limbic motor cortex, the anterior cingulate. This opens the possibility of two types of interventions. First, one may be able to modulate the embodied experience by enhancing insula reactivity where necessary, e.g. when engaging in risky behavior, or attenuating insula when exposed to drug-relevant cues. Several investigators have used real-time fMRI approaches to modify specific neural substrates, including the insula (Caria et al., 2007). Second, one may be able to reduce the urge to act by increasing limbic motor cortex processing, i.e. inhibiting the urge to use by employing cognitive training targeted at the anterior cingulate. There are three fundamental questions that need to be addressed in order to move the field forward. First, how does altered interoceptive processing contribute to the risk, recovery, and relapse of substance use disorders? Second, can interoceptive processing be used together with biological assessments as biomarkers of severity of substance use disorders? Third, is interoceptive processing amenable to intervention that alters risk, recovery, and relapse? Providing answers to these questions will determine whether interoception is as fundamental to drug addiction as disruptions of reward-related processing,

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Highlights

- Interoception is the processing and integration of body afferents
- Insular cortex is the central hub for processing interoception
- Insula dysfunction has been reported in several addictive disorders
- Inadequate interoceptive processing contributes to dysfunctions in approach and avoidance behaviors
- Insular modulation may provide a new treatment approach for addiction