Review

Neurobiology

On the Role of Insula in Drug Addiction

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Drug addiction is a chronic, relapsing brain disease with limited treatment options and a high recurrence rate. Neuromodulation techniques, including repetitive transcranial magnetic stimulation, transcranial direct current stimulation, and deep brain stimulation, hold great therapeutic promise in the treatment of drug addiction. The insula is a key brain region in drug addiction, and its value as a neuromodulatory target in drug addiction needs further exploration. This article presents preclinical and clinical evidence for the role of the insula in drug addiction and explores its promise as a target for the treatment of drug addiction.

Keywords: Insula; Neuromodulation; Drug Addiction; Deep Brain Stimulation; Mechanism

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DRUG addiction is a chronic relapsing brain disorder characterized by compulsion to seek and take drugs, loss of control in restricting drug intake, and negative emotional states e.g., restlessness, anxiety, and irritability (1). Drug addiction has been becoming a serious public health and social problem. Addictive drugs not only directly damage the body's physiological functions and threaten life, but also cause obvious cognitive, emotional, and mental abnormalities, and even lead to suicide. All these related to drug addiction and the illegal and criminal behaviors caused by them have brought great social harm (2).

Treatment options for drug addiction are very limited, mainly including medications and behavioral psychotherapy, but the relapse rate is still extremely high. Studies have shown that neuromodulation techniques targeting specific brain regions have significant potential in the treatment of drug addiction (3). This paper reviews the drug addiction-associated neural network, the insula, as a potential neuromodulatory target for the treatment of addiction.

Neurobiological Mechanisms of Drug Addiction

Drug addiction is divided into three phases: repeated periodic indulgence or intoxication, withdrawal or negative emotion, focus or anticipation (craving), and worsening over time, involving brain reward, stress, and neuroplastic changes in the executive function system (4). Indulgence/intoxication phase involves changes in dopamine and opioid peptides in the basal ganglia; withdrawal/negative mood phase involves decreased function of the dopamine component of the reward system and recruitment of brain stress neurotransmitters in pan-amygdala neural circuits; focus the anticipation (craving) phase involves dysregulation of key afferent projections from the prefrontal and insular cortex to the basal ganglia and pan-amygdala (5).

The neurobiological mechanisms involved in the various stages of drug addiction can be conceptualized as changes in brain regions or nuclei, especially specific brain circuits. The nucleus accumbens is currently the most studied target in treatment-resistant addicts (6), but other brain regions or nuclei that

play differently important roles in the development of drug addiction are also promising targets, such as the insula (7). Further exploration is needed to determine its clinical application value.

Insular Function and Its Network Connectivity in Addiction

The insula is a triangular neocortex located below the Sylvian fissure, located between the piriform cortex, orbital cortex, motor cortex, sensory cortex, and auditory cortex (8). The insula is divided into two parts: the larger part at the front, called the anterior insula, and the smaller part at the back, called the posterior insula. From the cell structure, the insula was identified as having three regions: the anterior non-granular region, the posterior granular region, and the middle granular-poor region (9). The insula covers only 2% of the cerebral cortex, yet it acts as a functionally highly diverse highway involved in homeostatic, cognitive, and affective processes (10). The insula is able to integrate and participate in such a wide range of functions because of its extensive network of connections. The anterior insula is mainly connected with the anterior cingulate area, frontal area, orbitofrontal area, and anterior temporal area, while the posterior insula is mainly connected with the posterior temporal area, parietal area, and sensorimotor area (11). The insula connects many brain regions related to addiction and plays a key role in the development of drug addiction (12).

The Role of Insular Interception in Drug Addiction

The insula integrates input from a variety of physiological processes, including the airway, gut, cardiovascular, musculoskeletal, visceral, and immune systems, all of which are involved in the body's response to addictive behaviors. The function of the insula is to map the body's ongoing physiological state and play a direct role in survival and maintaining homeostasis (13). This process of mapping the body's internal state is called "interoception," and the insula is the center of interoception (14). Interoception is a crucial process of drug addiction; that is, through receiving, processing, and integrating body-related signals of external stimuli, it affects continuous motivational behavior and prompts individuals to approach or avoid drug abuse to a certain extent (15). The posterior insula maintains a constant record of the current state of the body; this information is then relayed through the thalamus and the granular-poor insula, which appear to integrate salient external stimulus information (16). The anterior insula maintains homeostasis by comparing the current state of the body and the environment with the previous state and environment, and ultimately guides behavior toward or away from these stimuli, indicating that the anterior insula plays an important role in drug-seeking behavior (17).

Insula: A Key Neural Region for Drug Addiction

Study has first found that an insular stroke can make tobacco addicts quit smoking immediately, which is characterized by easy and fast quitting, no relapse, and no urge to smoke after quitting (18). This finding was subsequently confirmed by two prospective studies. Compared with non-insular damage, insular damage increases the probability of successful smoking cessation but also increases the motivation to continue to quit (19). Compared with basal ganglia damage alone, the possibility of smoking cessation is greater, and the addiction score is lowered more, indicating that the insula plays a special role in smoking addiction (20). Yousefzadeh-Fard et al. (14) studied the impact of insular and basal ganglia strokes on heroin withdrawal and found that isolated basal ganglia strokes and isolated insular strokes reduced heroin use rates, and an insular stroke alone had a larger effect than a basal ganglia stroke alone. This finding confirms that, in addition to tobacco addiction, the insula is also a key neural region for opioid addiction (21).

In addition to studies on the relationship between insular lobe damage and addiction, considerable evidence has also been obtained from structural and functional imaging studies of the insular lobe of addicts. Compared with non-smokers, the thickness of the insular cortex and the density of gray matter in smokers were significantly reduced (22, 23). Cocaine dependence and the duration of dependence have been shown to be related to the reduction of insular gray matter volume (24, 25). Resting state functional connectivity (rsFC) is a method of measuring interbrain activity in the resting state that is used to study the neural circuits of addiction (26). Studies have confirmed that smokers reduce the rsFC between the right anterior insula and the right superior frontal gyrus (27, 28). Smokers have lower rsFC between the insula, executive function area, and superior frontal gyrus (29). Cocaine users have reduced connections between the left and right insula and the dorsal anterior cingulate gyrus, thereby affecting the salience network (30, 31). The salient network connectivity of alcohol users is lower than that of the control group, and the insular blood flow is weakened (32). Non-resting state studies have shown that the activity of the insula is more active in smokers in the context of smoking cues compared with neutral cues (33). Substance-dependent individuals using cocaine, alcohol, or nicotine showed that, relative to neutral cues, BOLD signaling for addictive substance cues is in three distinct clusters (medial prefrontal cortex/anterior cingulate gyrus, left inferior frontal gyrus/insula, and right anterior motor cortex) and is significantly increased (34).

In addition, the insula is involved in the addictive behavior of multiple addictive animal models. Studies using different animal models of addiction and different manipulation measures and experimental paradigms have shown that the insula is involved in the addictive behavior of multiple addictive substances in different aspects (35, 36).

Using the conditioned place preference (CPP) protocol, anisomycin was injected into the anterior insula or posterior insula of amphetamine-CPP rats after conditioned amphetamine context memory activation, and amphetamine-CPP expression was lost (37). In the extinction experiment, the expression time of amphetamine-CPP was reduced in the posterior insula after reversible inactivation (38). Lidocaine inactivated the insular lobe of amphetamine-trained rats and prevented the impulse of rats to seek amphetamine in a place preference task (39). Ibotenic acid selectively damages the mouse insula to prevent nicotine-induced CPP (40, 41).

Under a self-administration paradigm, inactivation of the anterior insula of rats by a mixture of baclofen and musmol attenuated drug-environment-induced recovery of co-

caine-seeking behavior without altering locomotor activity (42). In rats subjected to cocaine self-administration training followed by extinction experiments, the relapse test showed that inactivation of the anterior insula reduced cue-induced relapse (43). Inactivation of the agranular cortex in nicotine-self-administered rats reduced nicotine intake without affecting food intake and also prevented cue-induced relapse of nicotine-seeking behavior (44, 45). Local injection of D1-receptor antagonists in the anterior insula leads to a sustained reduction in nicotine self-administration and can also reduce cocaine intake (46).

In general, the insula is a basic area for the acquisition, maintenance, and relapse of drug addictive behaviors, and the interoceptive function of the insula plays a pivotal role in drug intake, withdrawal, and relapse. In the future, the anterior insula can be further explored, as can the different roles of the posterior insula in different drugs and animal models.

Insula: Neuromodulatory Target for Drug Addiction.

Current treatments for drug addiction are limited and have a high failure rate. Functional neurosurgery, such as cingulotomies, anonymity, and nucleus accumbens destruction, can significantly reduce the symptoms of drug addiction, but it has been rejected due to its possible serious psycho-emotional complications and ethical risks (47). Neuromodulation techniques have shown promising potential in the treatment of neuropsychiatric disorders, including drug addiction. There are abnormalities in neural circuits in drug addiction, and neurostimulation technology can restore normal brain function through local stimulation of the target area, thereby inhibiting addictive behaviors (48). As an important part of the mesolimbic reward system, the role of the nucleus accumbens as a brain stimulation target area in the treatment of drug addiction has been evaluated and confirmed by animal and clinical studies, but it still cannot solve all drug addiction problems (49). At present, there is no more definite clinical double-blind trial evidence. In view of the important role of the insula in drug addiction, especially its close connection with known addiction-related brain areas, the insula is worth exploring as another target area for the treatment of drug addiction.

First of all, transcranial magnetic stimulation (TMS) insular lobe treatment of drug addiction: TMS is a non-invasive brain stimulation technique that alters magnetic fields to generate electrical currents in targeted brain regions (50). The basic principle of TMS is that a brief current is passed through a magnetic coil to generate a momentary high-intensity magnetic pulse. This pulse generates an electric field in the target cortical area, which can induce depolarization of superficial cortical neurons located below the coil and affect cortical excitability (51). Various shapes of magnetic coils have been developed to affect neural activity and excitability in different brain regions: (i) circular coils, which are powerful but not focused; (ii) "figure-eight" coils, which consist of two newly developed H-shaped coil can stimulate deeper structures without excessive field strength or low focus (52). The research on TMS in addiction mainly focuses on the prefrontal cortex, especially the dorsolateral prefrontal cortex (dlPFC) (53), and there are relatively few studies on the insula. Recently, Dinur-Klein and coworkers conducted a randomized, double-blind, placebo-controlled study, demonstrating that in the short term, high (10 Hz) rather than low (1 Hz) frequency targeted the bilateral dlPFC and insula (54). Deep TMS can reduce the number of cigarettes smoked, reduce smoking levels, nicotine dependence, and increase short-term and long-term smoking cessation rates. This study suggested that targeting the insula in addition to the dlPFC may be the key to better long-term outcomes. Moreover, a multicenter double-blind RCT included 262 chronic smokers who met the DSM-5 criteria for tobacco use disorder and who had already tried unsuccessfully to stop smoking at least once, with 68% having tried at least three times. The lateral prefrontal and insular cortices underwent daily bilateral active or sham rTMS for three weeks, followed by three weeks of once weekly rTMS, and found that stimulation of relevant brain circuits like insula is an encouraging method (55). The above reports suggest that the insula can be considered a promising neuromodulatory target for TMS treatment of addiction, and further studies are needed.

Second, transcranial direct current stimulation (tDCS) for insular lobe treatment of drug addiction: tDCS is a non-invasive, painless, and safe method of brain stimulation that uses a low-voltage, relatively weak current (56). tDCS is thought to regulate brain activity through two mechanisms: (i) by altering the resting membrane potential of neurons, depolarizing neurons near the anode and hyperpolarizing neurons near the cathode; and (ii) by regulating synaptic activity in a manner similar to long-term potentiation (LTP) at the anode and long-term depression (LTD) at the cathode (57). Therefore, the regulatory effect depends on the strength, duration, and direction of the current, where excitability increases with anodal tDCS and cathodal tDCS contributes to hyperpolarization and inhibition (58).

The research on the target of tDCS in the treatment of drug addiction is mainly dlPFC (59), and there are relatively few studies directly targeting the insula in the treatment of drug addiction. In a clinical study, tDCS in the frontal-parietal-temporal region significantly reduced daily cigarette consumption in smokers, and tDCS in the frontal-parietal-temporal region affected the activity of many brain regions, including the interoceptive function of the insula, the associative memory function of the hippocampus, and the cognitive function of the lateral prefrontal cortex, etc., thereby reducing smoking behavior (60). The excitatory effects of electrical stimulation of the dlPFC region can have downstream, secondary effects on other cortical and subcortical structures, including the medial prefrontal cortex, amygdala, and insula (61). Given the functional connection between the dlPFC and the insula, changes in insular activity or function induced by tDCS directly targeting the dlPFC may play a role in the process of drug addiction (62), which also suggests that electrical stimulation therapy targeting the insula can alleviate the addictive behavior of drug addiction, of course, more targeted research is needed.

Third, deep brain stimulation (DBS) of the insular lobe for drug addiction: DBS is an adjustable, reversible, non-destructive neurosurgical intervention that uses implanted electrodes to deliver electrical impulses to various regions of the brain and regulate abnormal neural networks (63). The nucleus accumbens, subthalamic nucleus, dorsal striatum, lateral habenula, medial

prefrontal cortex, and hypothalamus have been studied as DBS targets for drug addiction (64). Pushparaj et al. found that under two self-administration reinforcement paradigms, high-frequency electrical stimulation of the insula significantly reduced nicotine uptake as well as nicotine-seeking behavior induced by cues and ignition, while there was no apparent effect on food intake (44). Further detection of insular lobe brain slices showed that high-frequency electrical stimulation can inactivate insular lobe neurons. Continuous DBS in the anterior insula can inhibit the recurrence of morphine CPP in rats and promote its regression (65). In a study, in which DBS targeted regions ranging from the lateral orbitofrontal cortex to the dorsal portion of the agranular insula, showed that high-frequency DBS blocks the acquisition of morphine preference, promotes extinction of morphine preference, and prevents drug-induced morphine igniting (66).

The advantages of DBS over rTMS or tDCS include: (i) DBS can go deeper into deep brain regions and is highly focused because many addiction-related regions are located deep in the brain; (ii) DBS can achieve continuous and uninterrupted stimulation after implantation, which can achieve long-term treatment because addiction is a chronic recurrent brain disease and the effect of electrical stimulation of neurons is time-dependent, that is, long-term stimulation can achieve long-term therapeutic effects; (iii) The application of DBS treatment is the basis for addiction research; and (iv) It can be remotely controlled for the stimulation parameters, optimized the treatment plan, and detected changes in stimulation parameters in real time. However, choosing an invasive treatment method will always cause ethical issues, but for extremely severe cases that are difficult to cure, such as some diseases of addiction that carry serious individual and social harm, surgery may be the best option especially when there is no truly effective treatment.

Conclusion

Drug addiction involves a wide network of brain regions and a variety of neural circuits, and the dysfunction of related brain regions and the disorder of neural circuits promote the continuous development and deterioration of drug addiction. Stimulating a specific brain region can affect the functional connectivity of the neural circuits under the region, causing changes in neurotransmitters in the brain region and normalizing the pathological brain functional network. The insula can be used as a new target for the treatment of addiction because it is a key brain area of drug addiction, has rich structural and functional connections with reward system-related brain areas, and is a part of the drug addiction network. Insula is a promising neuromodulatory brain region that could be a stimulating target for the treatment of addiction. As a relatively mature technology for the treatment of neurological diseases, DBS has been applied to treat drug addiction and has achieved promising results.■

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