# Structural and Functional Abnormalities of the Insula in Addiction

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## Abstract

The insula is located deep within the lateral sulcus of the brain and is involved in various psychological functions including emotion and interoception. Structural changes in the insula and abnormal functional connectivity observed in addiction underscore its role in addictive disorders, and neuromodulation of the insular region for addiction intervention has emerged as an area of growing research interest. Future studies should employ fine-grained parcellation of the insula and integrate multiple methodologies to further investigate the specific mechanisms through which the insula contributes to addiction, while also delineating the commonalities and distinct characteristics across different addiction types, thereby facilitating the development of more effective brain-based interventions for addiction.

## Full Text

## Structural and Functional Abnormalities of the Insula in Addiction

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## Abstract

The insula, located deep within the lateral sulcus, is involved in multiple psychological functions including emotion and interoception. Structural changes and functional connectivity abnormalities in the insula among individuals with addiction demonstrate its critical role in addictive behaviors, and stimulating the insular region to intervene in addiction has gradually become a focus of research attention. Future studies should further investigate the specific roles of insular subregions in addiction through fine-grained parcellation and the integration

of multiple methods, while exploring both commonalities and distinct characteristics across different addiction types to facilitate more effective brain-based interventions for addiction.

**Keywords:** insula, addiction, intervention, functional connectivity, brain imaging

The human insular cortex (IC) is situated deep in the lateral sulcus and represents a crucial brain region governing diverse cognitive and emotional functions (Mesulam & Mufson, 1982; Deen et al.,2011; Kelly et al., 2012). The insula maintains important bidirectional connections with the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), somatosensory cortex, and subcortical structures including the amygdala, globus pallidus, and thalamus (McDonald, Shammah-Lagnado, Shi, & Davis, 1999; Shi & Cassell, 1998). Given its involvement in various addictive behaviors, the insula has been termed the "hidden island of addiction" in the human brain (Naqvi & Bechara, 2009).

## 1. Subregional Structure and Functional Differentiation of the Insula

Recent in vivo imaging and lesion studies utilizing electrophysiological techniques, positron emission tomography (PET), and functional magnetic resonance imaging (fMRI) have demonstrated that the insula integrates affective, cognitive, and sensorimotor systems, exhibiting broad functional capabilities (Kurth, Zilles, Fox, Laird, & Eickhoff, 2010; Nieuwenhuys, 2012; Pavuluri & May, 2015). It serves as a hub for regulating social cognition (Menon & Uddin, 2010), empathy (Fan, Duncan, de Greck, & Northoff, 2011; Klimecki, Leiberg, Ricard, & Singer, 2014), reward-driven decision-making (Bartra, McGuire, & Kable, 2013; Hauser, Iannaccone, Walitza, Brandeis, & Brem, 2015; Preuschoff, Quartz, & Bossaerts, 2008), emotion (Kaczkurkin et al., 2017; Wise et al., 2017), and somatic pain processing (Craig, 2003; Wiech, Jbabdi, Lin, Andersson, & Tracey, 2014). As a critical neural center for interoceptive processing systems, the insula plays an essential role throughout the formation, maintenance, withdrawal, and relapse processes of addiction (Droutman, Read, & Bechara, 2015).

As a specialized brain region participating in numerous cerebral activities with extensive functions, the insula exhibits pronounced heterogeneity and an anterior-posterior distributed organization. To more clearly characterize this functional and structural differentiation, previous researchers have parcellated the insula into subregions based on its functional and structural characteristics (as shown in Figure 1 [Figure 1: see original paper]). Currently, the two most established parcellation approaches include: (1) an anatomical segmentation based on cytoarchitectonic composition, dividing the insula into the anterior-ventral agranular insula (AI), the posterior-dorsal granular insula (GI), and the intermediate dysgranular insula (DI) (Mesulam & Mufson, 1985); and (2) a resting-state functional connectivity (rsFC) analysis that divides the insula into three functional subregions: the posterior insula cortex (PIC),

dorsal anterior insula cortex (dAIC), and ventral anterior insula cortex (vAIC) (Chang, Yarkoni, Khaw, & Sanfey, 2013). Notably, structural and functional subdivisions do not completely overlap, and sufficient research is still lacking to provide detailed explanations for these differences. Nevertheless, both structural and functional approaches reveal an anterior-posterior differentiation pattern. This differentiation primarily manifests as the posterior insula being more responsible for perceptual activities such as sensorimotor processing, pain, and language processing, whereas the anterior insula is more involved in higher-level cognitive and executive functions (Chang, Yarkoni, Khaw, & Sanfey, 2012). Continuous information exchange between anterior and posterior insular regions enables functional integration. Generally, the anterior insula shows stronger functional connectivity with frontal lobes, while the posterior insula exhibits stronger connectivity with parietal lobes (Gasquoine, 2014).

The posterior insula sends projections to the caudate nucleus, thalamus, and somatosensory cortex (Shi & Cassell, 1998), and receives input from associative cortices in the parietal, occipital, and temporal lobes, playing an important role in the integration of pain, language processing, and sensorimotor functions (Chang et al., 2013). Its granular region serves as a multimodal convergence area for sensory information, processing exteroceptive information (e.g., touch, temperature, and pain), interoceptive information (e.g., visceral bodily sensations) (Craig, 2002, 2003), auditory information (Bamiou, Musiek, & Luxon, 2003), and vestibular information (Brandt, 1999).

The anterior insula cortex (aIC) projects to the caudate nucleus, nucleus accumbens (NAcc), and amygdala, while interconnecting with the basolateral amygdala (BLA) and prelimbic cortex (Gerfen & Clavier, 1979; Saper, 1982; Vertes, 2004). The anterior insula receives input from the medial portion of the mediodorsal thalamic nucleus and various other medial thalamic nuclei involved in motivational and affective functions of interoceptive sensation (Krettek & Price, 1977; Van der Werf, Witter, & Groenewegen, 2002). Connections between bilateral anterior insula and limbic system regions such as the anterior cingulate cortex constitute the "salience detection" network, known as the salience network (Seeley et al., 2007).

The insula-generated feeling states determine the relative salience of stimuli and allocate cognitive resources according to priority (Menon & Uddin, 2010; Uddin, 2015). The dorsolateral prefrontal cortex (central executive network) receives salience information from the anterior insula and processes it accordingly to control cognitive processes such as attention and working memory (Menon & Uddin, 2010), enabling us to attend to and remember salient events related to self-stability and emotional feelings (Chun & Turkbrowne, 2007; Dolan, 2002). In summary, the anterior insula identifies salient information from broad sensory stimuli and facilitates further processing of this information by accessing attentional and working memory resources in the brain (Mesulam & Mufson, 1985; Uddin, 2015).

The interaction between anterior and posterior insula constitutes the integration of insular functions, unified under the concept of "interoception" (Craig, 2002). Interoception is a process that integrates internal signals and external stimuli to maintain homeostasis (Craig,2003), proceeding from posterior to anterior insula. Interoceptive signals first reach the posterior insula, considered the primary interoceptive cortex that processes low-level sensory features (Harrison, Gray, Gianaros, & Critchley, 2010). This signal is then transmitted to the anterior insula, where interoceptive information is integrated into conscious emotional feelings (Craig, 2009; Critchley et al., 2004) and projected to the basolateral amygdala, nucleus accumbens, anterior cingulate cortex, and OFC to jointly regulate affect, motivation, social functioning, and executive functions (Critchley, Wiens, Rotshtein, Ohman, & Dolan, 2004).

**Figure 1. Functional Differentiation of Insular Subregions in Addiction**

The functional and structural differentiation characteristics of the insula enable us to explore its role in addiction through subregional studies. During the initial stages of addiction formation, the insula participates in affective learning processes that interoceptively associate drug effects with environmental contexts. During drug use, interoceptive signals related to hedonic experience first reach the posterior insula, activating the primary interoceptive cortex and processing low-level sensory features. Subsequently, signals are transmitted to the anterior insula, where high-level interoceptive representations (or somatic state patterns) reach conscious awareness and are processed by memory-related regions (e.g., hippocampus). When individuals encounter environmental drug stimuli or cues, the dorsal anterior insula participates in recalling previously stored somatic state patterns associated with drug experience, which are represented through the ventral anterior insula and transmitted to the nucleus accumbens, thereby triggering subjective craving and drug-seeking behavior in addicts (Droutman, Read, & Bechara, 2015).

## 2. Structural and Functional Changes of the Insula in Addiction

### 2.1 Structural Changes of the Insula in Addiction

It is unsurprising that the insula, as a key region supporting interoception, is involved in all major aspects of addiction. Naqvi et al. (Naqvi, Rudrauf, Damasio, & Bechara, 2007) first noted the insula' s important role in addiction. They found that smokers with insular lesions were more likely to become addicted than control groups, yet could quit smoking more easily without relapse and experienced no urge to smoke after quitting. Subsequent brain lesion studies indicated that insular damage best predicted smoking cessation success, with the probability of quitting being five times higher than when the insula remained intact (Suner-Soler et al., 2012). Additional research showed that smokers with insular lesions experienced fewer smoking urges (Abdolahi et al., 2017) and less

severe withdrawal symptoms after quitting (Abdolahi et al., 2015). Animal studies also demonstrated that nicotine exposure alters the structure and function of insular synapses, which appears essential for maintaining continued smoking behavior and developing nicotine addiction (Naqvi, Gaznick, Tranel, & Bechara, 2014; Slotkin, 2002). Furthermore, subsequent studies revealed that damage to adjacent basal ganglia structures (such as the putamen region of the striatum) also leads to smoking cessation. Gaznick et al. (Gaznick, Tranel, McNutt, & Bechara, 2014) found that both basal ganglia lesion groups and combined insular-basal ganglia lesion groups showed significantly higher and more sustained smoking cessation rates than groups with lesions in other brain regions: 37% of the basal ganglia lesion group remained abstinent at 12-month follow-up, while the combined insular-basal ganglia lesion group showed even better cessation outcomes, with 75% remaining abstinent at 12-month follow-up.

Substantial evidence indicates that compared to non-smokers, smokers exhibit significantly reduced cortical thickness and gray matter density in the insula (Brody et al., 2004; Fritz et al., 2014; Stoeckel, Chai, Zhang, Whitfield-Gabrieli, & Evins, 2016), particularly in the left insula (Sutherland et al., 2016). Smokers show lower gray matter density in the left anterior insula extending to the inferior frontal and temporal cortices, which correlates negatively with daily cigarette consumption (Stoeckel et al., 2016). Bilateral anterior insular gray matter volume negatively correlates with scores on the Fagerström Test for Nicotine Dependence (FTND) (Wang et al., 2019), suggesting that more severe nicotine neurotoxic damage to anterior insular cortex corresponds to higher nicotine dependence. From an age perspective, older smokers (30-49 years) show more pronounced changes in insular cortical density compared to younger smokers (20-29 years) (Hanlon et al., 2016). However, among younger smokers (16-21 years), no significant group differences in insular thickness were observed compared to non-smokers, though smoking duration negatively correlated with right insular thickness, and both smoking dependence and urges negatively correlated with right ventral anterior insular cortical thickness (Morales, Ghahremani, Kohno, Hellemann, & London, 2014). This may suggest that insular structural changes result from long-term smoking.

Although most research on the insula-addiction relationship has focused on nicotine, other addictive behaviors have also been shown to involve the insula, generally pointing to reduced insular volume and density. For instance, ischemic stroke patients with insular damage were more likely to discontinue opioid use before and after stroke onset, with this effect being more pronounced in younger patients (Yousefzadeh-Fard et al., 2013). Cannabis users show decreased bilateral insular cortical thickness (Lopez-Larson et al., 2011), and compared to occasional users, frequent cannabis users exhibit reduced left insular gray matter volume that correlates with cannabis use frequency during the three months preceding the study (Battistella et al., 2014). Cocaine users have thinner insular cortex compared to healthy controls (Geng et al., 2017), and longer cocaine dependence duration correlates with greater gray matter volume reduction in the insular cortex (Barros-Loscertales et al., 2011). This reduction in insular gray

matter volume is associated with greater cocaine use impulsivity (Ersche et al., 2011). Heroin-dependent individuals show smaller gray matter volume in the right posterior insula (Gardini & Venneri, 2011), and individuals dependent on stimulants show significant gray matter reduction in the left insula (Ersche et al., 2013). Similarly, methamphetamine users exhibit reduced bilateral insular gray matter density (Schwartz et al., 2010), with greater effects in the left insula (Morales, Lee, Hellemann, O' Neill, London, & dependence, 2012).

Alcohol consumption also induces changes in insular gray and white matter. Alcohol-dependent patients show bilateral insular gray matter atrophy (Yang et al., 2016), with bilateral anterior insular volume reduced by 10% in alcohol-dependent individuals (ages 22-56) compared to healthy volunteers (Senatorov et al., 2014). Among adolescent subjects recruited from alcohol addiction treatment, insular white matter volume increased and correlated with binge drinking frequency over one year, while right insular white matter volume enlargement correlated with alcohol craving (Chung & Clark, 2014). Regarding gray matter, a 10-year follow-up study found that heavy-drinking adolescents without alcohol use disorder showed significantly smaller right insular gray matter volume compared to light drinkers (Heikkinen et al., 2017). Interestingly, analysis of three neuroimaging samples (N = 2,423) spanning childhood/adolescence to middle age revealed that smaller insular volume was associated with increased alcohol use, appearing to be a genetic risk factor predisposing to increased drinking rather than a consequence of alcohol consumption (Baranger et al., 2020).

In behavioral addictions, individuals with Internet gaming disorder (IGD) show significantly reduced left insular gray matter density and right insular white matter density (Lin, Dong, Wang, & Du, 2015). IGD-related insular gray matter atrophy correlates positively with IGD severity (Weng et al., 2013). IGD youth show increased cortical thickness in bilateral insula and right inferior temporal gyrus, with left insular cortical thickness in IGD patients correlating significantly with symptom severity (Wang et al., 2018). A study of excessive social media users found that bilateral posterior insular gray matter volume negatively correlated with social media addiction symptoms (Turel, He, Brevers, & Bechara, 2018). Similarly, individuals with smartphone addiction (SPA) show significantly reduced left anterior insular gray matter volume compared to controls (Horvath et al., 2020).

In gambling addiction research, results suggest that distorted cognitive processes related to event sequences may be supported by the insula. Individuals with higher levels of gambling-related cognitive distortions show larger right insular gray matter volume (Lu, Kong, & Kong, 2019; Noel, Brevers, & Bechara, 2013). While healthy controls and patients with lesions in other brain regions show strong "near-miss" effects and exhibit typical gambler' s fallacy, patients with insular lesions do not display these behaviors. Interventions that reduce insular reactivity may hold promise for treating gambling addiction (Clark, Studer, Bruss, Tranel, & Bechara, 2014).

In summary, these findings demonstrate that the insula undergoes structural

changes in addicted individuals, with most results pointing to reduced insular gray matter volume and density, thereby establishing its relationship with addiction.

### 2.2 Abnormal Functional Connectivity of the Insula in Addiction

Across various addictions, insula-centered network functions and their functional connectivity generally show reduced characteristics. Smokers exhibit decreased resting-state functional connectivity (rsFC) between the right anterior insula and right superior frontal gyrus (Fedota, Matous, Salmeron, Gu, Ross, & Stein, 2016). Additionally, compared to non-smoking controls, smokers show significantly reduced rsFC between the insula and OFC, superior frontal gyrus, and temporal lobe, while rsFC between the insula and OFC, temporal lobe, and occipital lobe positively correlates with FTND scores, and rsFC between the insula and anterior ACC negatively correlates with FTND scores (Zhou et al., 2017). In nicotine withdrawal studies, relapsers show weaker rsFC between left and right insula and bilateral precentral/postcentral gyri compared to non-relapsers, suggesting that relapse vulnerability is associated with weaker connectivity between posterior insula and primary sensorimotor cortex (Addicott, Sweitzer, Froeliger, Rose, & McClernon, 2015). A study comparing resting-state BOLD data before and after 48-hour smoking cessation, using three right-hemisphere insular regions (dorsal, ventral, and posterior) as seed points, found that overall dynamic resting functional connectivity decreased during abstinence. Specifically, dorsal and posterior insula showed enhanced connectivity with default mode and salience networks, while ventral insula showed reduced connectivity with the executive control network. Furthermore, rsFC between ventral and posterior insula seeds significantly correlated with subjective aversion and withdrawal symptom scores (Fedota et al., 2018). One study found that increased risk-taking in smokers correlated with enhanced rsFC in dACC-rAI, dACC-lAI, and rAI-lAI due to stronger nicotine dependence, but was unrelated to risk-level activation (Wei et al., 2016). Non-resting-state studies also found that smokers participating in a memory retrieval task involving smoking and neutral cues showed greater left insular activity when retrieving smoking cues compared to neutral cues, and smokers exhibited stronger craving when viewing smoking cue images (Janes et al., 2015). Meta-analyses concluded that smoking cues elicit greater fMRI responses in the insula compared to neutral cues (Engelmann et al., 2012). Smoking cues induce stronger functional connectivity between left insula and right insula, OFC, and striatum, with higher nicotine dependence scores associated with stronger connectivity in related circuits (Claus, Blaine, Filbey, Mayer, & Hutchison, 2013).

In individuals dependent on prescription opioids, rsFC between anterior insula and anterior midcingulate cortex, putamen, and amygdala is reduced, with longer drug use duration associated with greater functional connectivity changes (Upadhyay et al., 2010). Cocaine users show reduced rsFC between left and right insula and between insula and anterior cingulate cortex, affecting the

salience network (Geng et al., 2017). Individuals who relapse to cocaine show weaker rsFC between posterior insula and putamen compared to non-relapsers (McHugh et al., 2013). Cocaine users exhibit significantly weaker functional connectivity between anterior insula and anterior cingulate cortex and striatum, with inter-network connectivity strength significantly correlating with greater unplanned impulsivity in cocaine users (Wisner, Patzelt, Lim, & MacDonald, 2013). Compared to placebo, nicotine administration also enhances brain responses in right anterior insula and striatal regions to reward or loss cues (Moran et al., 2018).

Compared to controls, alcohol addiction groups show stronger rsFC among striatum, insula, and anterior cingulate cortex (Kohno, Dennis, McCready, & Hoffman, 2017). Compared to placebo controls, regular drinkers show weaker connectivity between brain activity and dACC after alcohol consumption. Moreover, the more alcohol reduces right aINS-dACC functional connectivity, the calmer participants feel under alcohol' s influence, suggesting that reduced connectivity between these two salience network regions may be related to alcohol' s rewarding effects (Gorka, Phan, & Childs, 2018). Alcohol users show lower salience network connectivity during spatial working memory tasks, with reduced cerebral blood flow in the insula (Sullivan et al., 2013).

In behavioral addiction research, IGD subjects also show reduced functional connectivity between dorsal putamen and posterior insula (Hong et al., 2015) and between supplementary motor cortex and insula (Jin et al., 2016). Compared to healthy controls, the IGD group shows reduced functional connectivity between left posterior insula and bilateral supplementary motor areas, midcingulate cortex, and between right posterior insula and right superior frontal gyrus, indicating reduced functional integration among insular subregions (Zhang, Mei, Zhang, Wu, & Zhang, 2016). Internet gaming addicts show enhanced rsFC between anterior insula and anterior cingulate cortex, putamen, and angular gyrus, with IGD severity positively correlating with connectivity between anterior insula and angular gyrus, and between posterior insula and posterior cingulate gyrus. Additionally, duration of Internet gaming use positively correlates with connectivity between anterior insula and anterior cingulate cortex (Zhang et al., 2016). Another study found that casual gamers showed significant positive correlations in the striatum-middle frontal gyrus-insula neural pathway when facing gaming cues, an effect absent in gaming addicts, suggesting that inhibitory neuromodulation from putamen to prefrontal cortex in IGD patients disrupts the balance between reward comparison (striatum), control (prefrontal cortex), and interoceptive perception (insula) systems (Wang, Dong, Zheng, Du, & Dong, 2020). Prolonged smartphone use before bedtime affects sleep quality and daytime mental state, with studies finding that rsFC strength between left insula and right putamen, and between right insula and left superior frontal gyrus, middle temporal gyrus, fusiform gyrus, orbital inferior frontal gyrus, and right superior temporal gyrus positively correlates with pre-sleep smartphone use duration (Hobkirk et al., 2018).

In resting-state functional connectivity studies of gambling addiction, researchers found that gambling addicts without drug abuse problems show positive correlations between insular seed connectivity to default mode network regions and gambling addiction severity. Functional connectivity strength between left insular seed and medial prefrontal cortex, bilateral temporoparietal junction, and between right insular seed and posterior cingulate cortex, bilateral temporoparietal junction positively correlates with addiction severity (Kosuke, Toshihiko, Ryosaku, Toshiya, & Hidehiko, 2020).

In summary, numerous resting-state brain function studies have confirmed that altered insular functional activity is associated with addiction. Addiction leads to changes in salience network function and connectivity between the insula and executive function regions.

## 3. The Insula and Addiction Intervention

While evidence for the insula' s involvement in addiction is compelling, research translating this knowledge into treatments for addicted individuals remains limited.

Deep brain stimulation (DBS) may be an effective method for treating drug addiction. Over the past 15 years, numerous animal DBS studies targeting various drug abuses have been conducted, with most reports showing reduced drug-seeking behavior following stimulation (Wang, Moosa, Dallapiazza, Elias, & Lynch, 2018). Stimulation of the insular region significantly attenuates nicotine intake under reinforcement schedules, as well as cue- and priming-induced nicotine-seeking behavior (Pushparaj et al., 2013). However, published human experience with DBS for drug addiction is limited to a few promising case series or reports, requiring further animal and human research to establish DBS' s role in addiction treatment.

Repetitive transcranial magnetic stimulation (rTMS) is increasingly used to treat drug dependence (Diana, Raij, Melis, Nummenmaa, Leggio, & Bonci, 2017). In a within-subject double-blind pilot study of eight healthy subjects, bilateral insular regions were targeted using the H-Coil magnetic field coil method under rTMS, followed by PET measurement of dopamine level changes. All subjects underwent PHNO-PET scans before rTMS across three days (sham, 1Hz, or 10Hz). Results showed that low-frequency rTMS (1Hz) targeting insular cortex significantly reduced dopamine levels in the substantia nigra, sensorimotor striatum, and associative striatum. Replicating this study in smokers or alcoholics would be a logical next step to evaluate whether H-Coil stimulation of bilateral insula could serve as an addiction treatment option (Malik et al., 2018).

Meta-analyses have found that high-frequency rTMS has beneficial effects on cravings related to nicotine use disorder, though existing evidence does not adequately support rTMS efficacy in alcohol intoxication treatment (Maiti, Mishra, & Hota, 2017). One study recruited adults who smoked at least 20 cigarettes daily and had previously failed treatment (N = 115). Participants were ran-

domly assigned to receive high-frequency, low-frequency, or sham stimulation daily for 13 sessions, administered after smoking cues were presented or not presented. Deep transcranial magnetic stimulation targeted the lateral PFC and bilateral insula using the H-Coil method. Results showed that high-frequency deep transcranial magnetic stimulation significantly reduced cigarette consumption and nicotine dependence. However, this study did not specifically target the insula alone, making it impossible to determine whether clinical effects were mediated by the insula, PFC, or both (Dinur-Klein et al., 2014). In another double-blind, sham-controlled randomized trial with 56 alcohol-dependent patients, participants received 10Hz rTMS or sham stimulation (using H8 coil, five days per week for three weeks). The stimulation target was the insular cortex and bilateral covering regions, excluding the prefrontal cortex. Although craving and drinking behavior decreased significantly during treatment, no differences were observed between rTMS and sham groups; both groups showed increased drinking at post-treatment and 12-week follow-up. Overall, this study does not support rTMS efficacy targeting the insula in alcohol-dependent patients (Perini et al., 2020).

In behavioral addictions, although no stimulation studies specifically targeting the insula exist, previous studies have reported that rTMS and transcranial direct current stimulation (tDCS) can reduce gambling cravings or gambling-related symptoms. A single-session low-frequency rTMS study targeting the right DLPFC found that rTMS stimulation correlated with significant reductions in gambling urges (Sauvaget et al., 2018), though rTMS was ineffective in reducing gambling behavior itself (Rosenberg, Klein, & Dannon, 2013; Sauvaget et al., 2018). tDCS targeting the DLPFC can modulate GABA levels in gambling disorder patients (Dickler et al., 2018) and enhance decision-making capacity and cognitive flexibility (Soyata, Aksu, Woods, Iscen, Sacar, & Karamursel, 2019). Repeated tDCS stimulation of the DLPFC in gaming addicts reduced addiction symptoms, decreased gaming time, and improved self-control (Lee et al., 2019). Previous research indicates behavioral and neurophysiological differences between behavioral and substance addictions (Gomis, Thoma, Turner, Hill, & Pascual-Leone, 2019). Therefore, exploring cognitive and neurophysiological characteristics unique to behavioral addictions and developing separate brain stimulation approaches targeting regions associated with behavioral addiction represent worthwhile endeavors.

In conclusion, the insula possesses many key functions related to addiction, and addicted individuals show varying degrees of structural and functional alterations in this region. Extensive research results indicate that the insula is an extremely promising target region for addiction intervention. Advancing brain stimulation technologies now allow researchers to target the insula for addiction treatment, offering promising therapeutic prospects.

The insula' s important role in addiction is now evident. However, because its structure and function exhibit anterior-posterior heterogeneous distributed characteristics, research must examine its functionally and structurally differ-

entiated subregions to more deeply understand the insula' s role in addiction. While most addiction findings point to reduced insular gray matter volume and density, and insula-centered network functions and connectivity generally show weakening characteristics, some studies have found contradictory results. For example, some research found increased left insular cortical gray matter density in smokers (Zhang et al., 2011); cocaine dependence in cocaine users was associated with enhanced functional connectivity between right insula and dorsomedial prefrontal cortex, inferior frontal gyrus, and bilateral dorsolateral prefrontal cortex (Cisler et al., 2013); and compared to healthy controls, heroin addicts showed significantly enhanced left insular functional connectivity that positively correlated with heroin dosage (陈佳杰等, 2017).

These contradictory findings regarding the insula may relate to several factors. First, they may stem from the insula's inherent functional and structural heterogeneity—different insular subregions have distinct functions and participate in different functional networks, yet some of the contradictory studies did not differentiate insular subregions. Second, the insula is a region with typical dynamic functional changes; as the center of interoception and a hub for regulating different network resources, it monitors internal states to modulate the allocation of limited cognitive resources. Therefore, changes in interoceptive mechanisms (such as withdrawal or craving states) critically influence insular functional responses, yet the aforementioned studies did not address the interoceptive states of addicted individuals (黄小璐, 2018). Additionally, both commonalities and specificities across different addictions require consideration. Numerous studies demonstrate that long-term adaptive changes in the nervous system under addictive drugs form the basis of substance addiction behaviors. Compared to substance-dependent addictive behaviors, behavioral addictions occur without any ingested substance, so their dependent state formation primarily results from psychological mechanisms. Taking Internet gaming addiction and heroin addiction as examples, although Internet gaming addiction should be considered a psychiatric disorder of the same nature as heroin addiction (both involving brain structural and functional damage), its addiction level is lower than heroin addiction (brain damage 偏向于低级中枢, with smaller scope), and it has greater potential for treatment recovery or spontaneous remission (贺金波, 聂余峰, 周宗奎, 柴瑶, 2017). Even among substance addictions, different addictions have specific characteristics. Although trait impulsivity is considered a good predictor of substance use disorder treatment outcomes (Loree, Lundahl, & Ledgerwood, 2015), impulsivity features described by the UPPS model (urgency, lack of premeditation, lack of perseverance, and sensation seeking) differ across addictions. Recent research shows that high sensation seeking and lack of perseverance relate to problematic alcohol use (Thomsen et al., 2018), lack of premeditation predicts alcohol intake and binge drinking, while negative urgency predicts alcohol-related problems (Tran, Teese, & Gill, 2018). Smoking status and nicotine dependence severity significantly correlate with all impulsivity features, with lack of premeditation and positive urgency showing the strongest correlations with smoking status ($r = 0.20$, $r = 0.24$) (Kale, Stautz, &

Cooper, 2018). Furthermore, addiction interventions yield different outcomes across substances—meta-analyses found that high-frequency rTMS has beneficial effects on nicotine-related cravings, but existing evidence does not adequately support rTMS efficacy in alcohol addiction treatment (Maiti, Mishra, & Hota, 2017). Therefore, both commonalities and specificities across different addictions require further exploration through fine-grained insular parcellation and clarification of subjects' interoceptive states.

Moreover, multiple method combinations should be employed to examine the insula' s specific role in addiction. For example, combined rTMS and fMRI approaches have been used in depression (Zheng et al., 2020) and Parkinson' s disease (Bhat et al., 2018) research, and using fMRI to observe specific effects of brain stimulation on the insula in addiction intervention warrants investigation. Additionally, studies have found that drug-induced rsFC changes closely relate to nicotine withdrawal—varenicline and nicotine reduce amygdala-insula circuit rsFC strength, an effect not observed in non-smokers (Sutherland, Carroll, Salmeron, Ross, Hong, & Stein, 2013). Therefore, combining brain stimulation with pharmacological treatment for insular addiction represents a feasible approach.

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*Note: Figure translations are in progress. See original paper for figures.*