Review

Neurobiology

Comparison of Neural Circuitry Mechanisms between Internet Game Addiction and Heroin Addiction

Fuzhou Wang*

Group of Neuropharmacology and Neurophysiology, Division of Neuroscience, The BASE, Chapel Hill, NC 27510, USA

*: All correspondence should be sent to: Dr. Fuzhou Wang.

Author's Contact: Dr. Fuzhou Wang, MD, PhD, E-mail: fred.wang@basehq.org

DOI: https://doi.org/10.15354/si.23.re249

Funding: No funding source declared.

COI: The author declares no competing interest.

Internet game addiction and heroin addiction have many similar clinical manifestations, but whether they share similar neural mechanisms is yet clearly known. Based on MRI data, it was found that the two types of addictions have some damages in the same brain structure and function, and the four addiction-related circuits as cognitive control loop, reward prediction and pleasure loop, motivation drive and salience attribution loop, and learning and memory loop showed widespread and enhanced activation. However, the brain damage area of heroin addiction is biased towards the higher cognitive control circuit and reward circuit, and the scope of damage is wider showing the functional connectivity of the four circuits is reduced, while the brain damage of internet game addiction mainly occurs in relatively low-level memory-learning circuits and motivation circuits, and the scope of damage is also relatively narrow by indicating decreased functional connectivity only occurs between cognitive control and memory-learning circuits. This indicates that the neural mechanisms underlying the two types of addictive behaviors have both similarities and differences. This review compares above-mentioned four circuitry mechanisms between internet game addiction and heroin addiction to highlight the underlying neural similarities between them and provide insights into potential interventional strategies.

Keywords: Addiction; Internet Game; Heroin; Neural Mechanisms; Addiction Circuits

Science Insights, 2023 March 30; Vol. 42, No. 3, pp.857-866.

© 2023 Insights Publisher. All rights reserved.

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed by the Insights Publisher.

ALTHOUGH the term "addiction" is sometimes fraught due to its contentious and stigmatizing connotations, it serves as a useful shorthand herein to describe the ways in which drug abuse and other forms of compulsive behavior, such as internet gaming, can lead to profound changes with one's life. The inability to stop using drugs despite abundant proof of their negative effects is a key aspect of drug addiction. Drug dependence worsens as it takes control of life at the expense of interactions with colleagues, friends, and family (1). Internet game addiction displays a very similar situation as they

are unable to stop playing games despite ample evidence of their detrimental effects, and it intensifies as it takes control of player's life, sacrificing contacts with peers, family, and society (2).

Internet game addiction has been becoming a serious social problem, but there is still no definite conclusion about its clinical characterization. On the one hand, it can be classified as an addictive mental disorder because Internet addiction has similar symptoms to substance addiction, such as the prominence, withdrawal, tolerance, and impulsivity of addictive behaviors and impulsivity (3, 4). On the other hand, it is believed that if Internet addiction is an addictive mental disorder, there should be specific abnormalities or damages in the central nervous system, but the existing clinical evidence is obviously not sufficient (5, 6). For this reason, MRI has been used recently to investigate the neural mechanisms of Internet game addiction and to provide more objective evidence for solving this problem.

Internet game addiction and the most common subtype of substance addiction—heroin addiction share the features of addictive behaviors such as impaired cognitive and motivational functions, increased craving for addictive cues, preference for rewards over risks, and dysfunction of impulse control (7, 8), and the four neural mechanisms involved in addiction like reward circuit, memory-learning circuit, motivation circuit, and cognitive control circuit (9, 10). These conclusions not only help to explain some differences in the clinical manifestations of the two types of addiction but also provide the theoretical basis for the debate on the qualitative issues of Internet addiction.

Addiction-Related Cues Induce Strong Cravings

Craving is the psychological longing that addicts hope to re-experience the addictive behavior. Every time the craving is satisfied, it forms a reinforcement effect, which is the core feature of the maintenance and relapse of addictive behavior (11). Addiction-related cues refer to stimulus signals that repeatedly match addictive behaviors, such as internet game information for internet game addiction and heroin information for heroin addiction (12, 13). It is believed that addiction-related cues were the main triggers of craving (14). During the addiction or withdrawal period, once exposed to addiction-related cues, it may trigger the craving for addictive behaviors that eventually lead to the maintenance or relapse of addictive behaviors.

Heroin Cues Activate and Enhance Multiple Brain Regions in the Addiction Circuit

The activation of multiple brain regions in the four addiction circuits in heroin addicts was significantly enhanced when evoked by heroin-related cues (15). Short-term abstainers reported a significant increase in craving following exposure to heroin cues, whereas long-term comparisons did not, and the brain activation in the left medial prefrontal cortex and left inferior parietal lobule was adversely linked with abstinence duration suggesting that long-term abstinence may be beneficial for heroin-dependent individuals in terms of decreasing the saliency value of heroin-related stimuli and possibly lowering relapse vulnerability (16). Wei et al. discovered that during exposure to heroin-related cues, both methadone maintenance treatment (MMT) and protracted abstinence exhibited significantly increased brain activation in the left pallidum, middle occipital gyrus, postcentral gyrus, anterior cingulate cortex, middle cingulate cortex, inferior parietal lobule, superior parietal lobule, amygdala, hippocampus, right inferior temporal gyrus, and inferior frontal gyrus triangularis; and despite the long-term MMT compliance with the regimen, these patients consistently experienced higher levels of subjective cravings and cue-induced brain activation (17). This suggests that heroin cues are strong activators of the addiction-related neural circuitries.

Internet Game Cues Enhance the Activation of Multiple Brain Regions in the Addiction Circuit

The study of internet game addicts (IGAs) found a similar conclusion to that of heroin addicts, namely, that the activation of multiple brain regions in the four addiction circuits was significantly enhanced when induced by internet game-related cues. Under gaming distraction, the function of response inhibition was impaired in the IGAs, and players were unable to activate the right dorsolateral prefrontal cortex and superior parietal lobe to maintain cognitive control and attention allocation for response inhibition under gaming cue distraction (18). Sun et al. examined the effectiveness of diffusional kurtosis imaging in identifying changes to the gray matter in those with internet gaming addiction and found that game addict individuals showed increased gray matter volume in the right inferior, middle, and para-hippocampal gyri, but decreased gray matter volume in the left precentral gyrus suggesting that several variabilities in brain microstructure, which could affect the pathophysiology underpinning internet game addiction (19).

It can be seen that addiction-related cues can induce strong addiction cravings in both heroin addicts and IGAs, manifested in multiple reward loops, memory-learning loops, motivation loops, and cognitive control loops. Highly widespread activation-response patterns of brain regions may have a linkage as an addiction cue appears, the memory of addiction-related activities (a memory-learning circuit) is first awakened, which leads to a response to addictive behaviors followed by reward expectations (reward circuit) that induces a motivation to engage in addictive behaviors (motivational circuit), which eventually get the brain regions maintained a high degree of activation.

Cognitive Decision-Making Favors Rewards and Ignores Risks

Another typical feature of addiction is the bias towards the reward pursuit of addictive behaviors while ignoring their risks in cognitive decision-making (20). Behavioral studies have found that when performing the delay discounting and gambling tasks, compared with the control group, the addiction group showed an impulsive pursuit of immediate rewards while ignoring the long-term risk of loss (21, 22). Similarly, this also happened in Internet game and heroin addicts who prefer rewards and ignore risks when making decisions.

Reduction in the Activation Level of Brain Regions of the Cognitive Control Circuit in Heroin Addiction

Drug addiction is characterized by deficits in inhibitory control and stimulus-driven attention, which are connected to lower

levels of activation in the right inferior frontal gyrus (IFG). Goudriaan and coworkers found that when heroin addicts performed the Iowa gambling task, compared with the control group, the activation of some brain regions of the motivational circuit was enhanced while the activation of the cognitive control circuit was weakened indicating that behavioral results found that heroin addicts were more inclined to choose cards with high rewards comprised with high long-term risks, showing a higher impulsive pursuit of immediate rewards (23). The acute effects of heroin administration on IFG activity were examined in heroin-dependent patients and found that heroin significantly reduced right IFG activity during both successful response inhibition and oddball-driven attention allocation, but did not change right IFG activity during response inhibition after adjusting for the effect of attention allocation demonstrating that acute heroin treatment disrupts stimulus-driven attention allocation without modulating IFG activity specifically during reaction inhibition (24). The prefrontal cortex (PFC) is disrupted in addiction that accounts for compulsive drug use as well as the negative behaviors connected to addiction and the loss of free will, which was proven by neuroimaging data by indicating that the orbitofrontal brain activation in heroin users was higher, whereas the right prefrontal cortex activation was lower than in the comparisons (25).

Internet Game Decreases the Activation Level of Brain Regions of the Cognitive Control Circuit

Internet addicts showed lower activation of cognitive control circuits when performing a money choice task than controls. Studies showed that IGAs were more inclined to choose the "high benefits, and high risk" task, and the reaction time of choice was shorter, and the activation degree of the superior frontal gyrus and precentral gyrus was lower (26-28). Dong and colleagues investigated the task selection preference of game addicts, and obtained similar results consistent with the above-mentioned studies, i.e., IGAs chose more high-risk, high-reward options, which was accompanied by lower activation of the anterior cingulate gyrus, posterior cingulate gyrus, and middle temporal gyrus, and their decision-making responses were also significantly shorter than those of healthy subjects and showed reduced activation of the superior frontal gyrus and superior temporal gyrus (29).

Therefore, IGAs exhibit a brain activation pattern comparable to that of heroin addicts while doing tasks involving monetary rewards. One possible explanation is that when IGAs and heroin addicts are confronted with immediate rewards, they, on the one hand, have a higher motivation to obtain the rewards and, on the other hand, lack the rationality to suppress possible risks, so they choose impulsive decision-making in both situations (30).

Cognitive and Motivational Dysfunction

Behavioral and electrophysiological data have found that both IGAs and heroin addicts exhibit abnormal cognitive and motivational functions. MRI studies have further explored the neural mechanisms of these abnormalities and found that the two have both similarities and differences.

Heroin Addiction Caused Structural Atrophy and Reduced Functional Connectivity in Some Brain Regions Involved in Cognitive Control and Reward Circuits

The MRI study of heroin addicts found that some brain regions of their cognitive control loops - PFC and anterior cingulate gyrus (ACG) had thinner cortex and smaller gray matter volume. Denier et al. found that gray matter (GM) and both perfusion conditions (heroin and placebo) had a substantial positive connection in frontal regions, and heroin-associated perfusion was likewise inversely connected with GM in the inferior temporal gyrus on both hemispheres, demonstrating that reduced GM volume is positively associated with low perfusion within frontal areas in heroin-dependent patients (31). Shi and coworkers found that heroin users had significantly decreased cortical volume in the prefrontal cortex and mesolimbic dopaminergic regions at all parcellation levels, although numerous visual and somatosensory cortical regions had increased volume relative to comparisons at a more precise parcellation level. The length of heroin usage was adversely linked with prefrontal brain gray matter volume. These data imply that heroin addiction may be associated with alterations in gray matter and may be linked to damage or maladaptation of the inhibitory control, reward, visual, and somatosensory brain functions (32). Methadone maintenance therapy is frequently used to treat heroin addiction. After one year of methadone therapy, patients had lower GM volume in the bilateral insula, occipital lingual gyrus, right cingulate gyrus, middle temporal gyrus, left inferior parietal lobule, caudate nucleus, temporal, and occipital areas, as well as changes in the brain's resting neural network suggesting that long-term methadone use can cause harm to the GM's structural integrity and adaptive alterations in people with heroin use disorder's neural networks, primarily affecting emotional perception, spatial localization, working memory, and other associated abilities (33). Therefore, significant structural atrophy existed in important brain regions of the cognitive control circuit in heroin addicts, regardless of whether they were in the abstinence period or the treatment period.

The atrophy of brain structure related to motivational function mainly occurs in the reward circuit, i.e., nucleus accumbens (NAc) and ventral pallidum (VP). Study showed that lower inferior frontal gyrus gray matter volume, which raises the possibility of a direct test of impaired inhibitory control using specific behavioral tests indicating that as a whole point to substance-specific volumetric alterations in human psychostimulant or opiate addiction, with implications for optimizing biomarker and therapy identification by primary drug of abuse (34). As thus, damage to the brain region of the reward circuit may lead to negative emotions in heroin addicts. In order to relieve negative emotions and seek higher pleasure, the addicts will continue to increase the frequency and dosage of heroin use.

Studies have also found that heroin addicts have significantly reduced functional connectivity in many brain regions. The specific manifestations are as follows (**Figure 1**):

i. The functional connectivity of brain regions inside the cognitive control loop is reduced. Heroin addicts had left functional connectivity was reduced between the prefrontal cortex and the right anterior cingulate gyrus and bilateral mid-

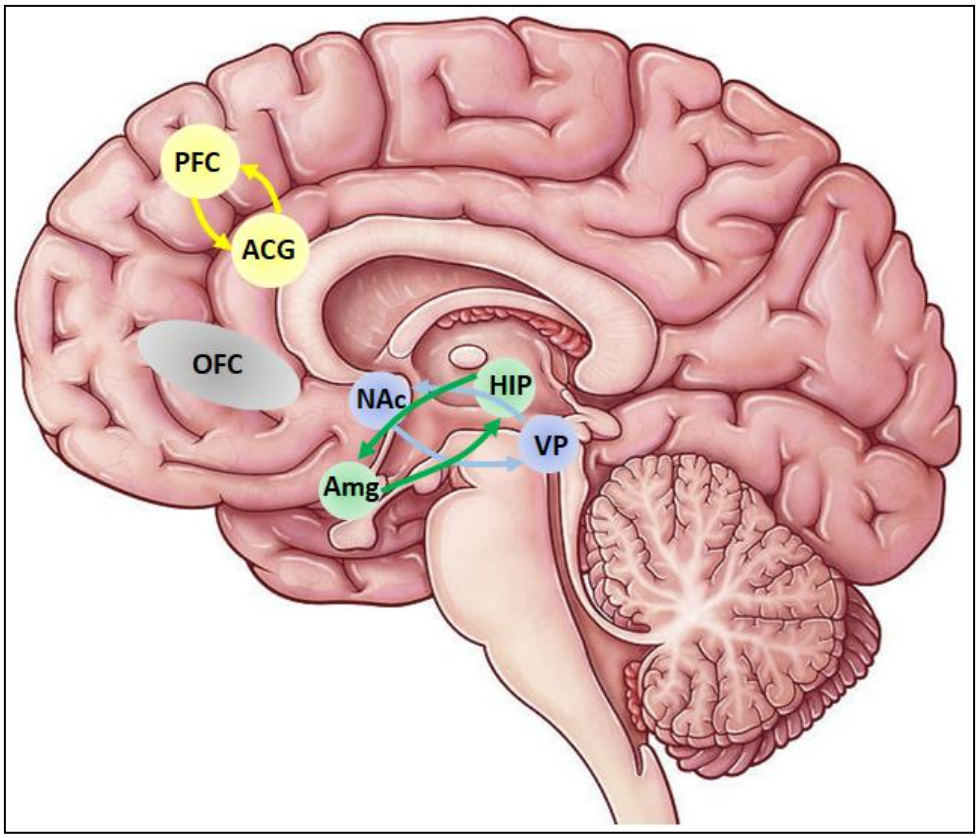

Figure 1. Interacting Brain Circuits Associated with Addition.
***Light Blue**: The Reward Circuit. A dopamine pathway from the ventral tegmental region to the nucleus accumbens (NAc, aka the ventral striatum), which then outflows via the ventral pallidum (VP). This route is involved in responding to incentives and directing behavior in their direction. **Light Green**: Learning and Memory Circuit. The hippocampus (HIP) is implicated in drug-related location memories, whereas the amygdala (Amg) is responsible for the emotional components of these memories. It is well recognized that drug-related memories are among the most potent and difficult to erase or eradicate. **Light Yellow**: Cognition Control Circuit. The anterior cingulate gyrus (ACG) and prefrontal cortex (PFC) are responsible for cognitive control and depend on a proper balance of glutamate and GABA interactions, allowing this region to exercise "top-down" regulation on the pleasure and motivation areas. **Gray**: Motivation Drive and Salience Attribution Circuit. The orbitofrontal cortex (OFC) evaluates the worth of rewards or salience and the use choice.*

dle frontal gyrus and between the right prefrontal cortex and the left middle frontal gyrus (35). Laboratory tests of cognitive-behavioral control were affected by substance use disorders, and individual variations in the functional connectivity between the NAc and the frontal cortical areas were linked to variations in the measures of cognitive-behavioral control (36). The prefrontal cortex is responsible for the inhibition of drug craving and cognitive control, and the decrease in its functional connectivity in the resting state directly leads to the persistence of addictive behavior and relapse after withdrawal.

ii. The cognitive control loop and memory-the functional connectivity of the learning loop-are reduced. In a study of 22 heroin-dependent and heroin-maintained outpatients and 17 healthy controls, researchers discovered that heroin acutely reduced fear-induced modulation of connectivity from the left fusiform gyrus to the left amygdala and from the right amygdala to the right orbitofrontal cortex in dependent patients, as well as positive correlations between the left fusiform gyrus to amygdala connectivity and different stress responses suggesting that in heroin-dependent patients, enhanced amygdala-related connectivity during scared face processing following placebo therapy transiently normalizes after acute heroin maintenance medication (37). Under control of head movement and GM volume of the right dorsolateral prefrontal cortex (DLPFC), resting-state functional connectivity of the right DLPFC indicated a significant decrease in interhemispheric DLPFC connection among people with heroin habit (38). The reduced functional connectivity between cognitive control and memory-learning circuits in

heroin addicts will make it difficult for them to rationally evaluate addiction-related cues and thus impulsively make irrational choices.

iii. The functional connectivity of the circuit with the reward circuit is reduced. The results showed that, compared with functional connectivity between the ventral anterior cingulate and NAc was reduced in heroin addicts compared to healthy subjects (39). The functional connectivity between the dorsal anterior cingulate gyrus and the caudate nucleus of the ventral striatum was significantly reduced in heroin addicts during withdrawal (40). The decreased functional connectivity between the brain reward and cognitive control circuits of heroin addicts will lead to a weakened ability to inhibit their compulsive drug-seeking behavior, resulting in uncontrolled heroin intake.

iv. The functional connectivity of memory-learning circuit to rewarding loop is enhanced. Zhai et al. studied 30 heroin addicts and 20 healthy subjects who had been withdrawn for more than 4 weeks to fill out the impulsivity measurement questionnaire and then performed fMRI scans and found that heroin addicts had increased coherence between the hippocampus, which represents the declarative memory system, and the non-declarative reward guided learning memory system, as well as a reduced intrinsic functional link between the hippocampus and the top-down control system, and this change was found to have behavioral significance over the behavioral index 'impulsivity,' as measured by the Barratt Impulsiveness Scale (41). The reward circuit is mainly responsible for the generation of euphoria in addicts, and the functional connection between it and the memory-learning circuit is enhanced so that heroin addicts in the withdrawal period form a stronger pathological reward memory. The activation and consolidation of the time will eventually be transformed into long-term memory, leading to the repeated appearance of relapse.

Internet Game Addiction Induces Structural Atrophy and Reduced Functional Connectivity in Some Brain Regions Involved in Motivation and Memory-Learning Circuits

MRI study on internet game addiction (IGA) did not draw the same conclusion as heroin addiction, and the brain structural abnormalities related to cognitive impairment are mainly manifested in the reduced gray and white matter density of the memory-learning circuit (hippocampus and amygdala). The hippocampus is one of the core brain regions responsible for learning and memory and the amygdala is related to emotional regulation and forms long-term memory traces for emotionally meaningful stimuli. An MRI study on 35 IGAs screened out by the IAT scale and 36 healthy subjects and found that IGA participants also showed significantly lower white matter density in the inferior frontal gyrus, insula, amygdala, and anterior cingulate than healthy controls, as well as significantly lower gray matter density in the bilateral inferior frontal gyrus, left cingulate gyrus, right precuneus, and right hippocampus (42). Ko et al. found that in comparison to controls, the subjects with IGA showed higher impulsivity and severity, lower GM density over the bilateral amygdala, lower FC with the left amygdala over the left DLPFC, lower FC with the right amygdala over the left DLPFC, and higher FC with the bilateral amygdala over the contralateral insula (43). The reduction of gray matter and white matter density in memory-learning circuit-related brain regions of IGAs will lead to their memory decline, poor academic performance, and negative emotions such as irritability and anxiety (44). The brain structural abnormalities associated with motivational impairment in IGAs are mainly manifested in the structural atrophy of some brain regions of the motivational circuit, such as the orbitofrontal cortex where goal-directed behavior produced by assessing the importance of current stimuli and predicting possible consequences, and its abnormalities are associated with addicts' craving for addiction-related stimuli, deviating decision-making intentions, and impulsive behavior (45).

Different from heroin addicts, the functional connectivity abnormalities of the four loops in IGAs are only manifested in two aspects:

i. The functional connectivity of brain regions inside the cognitive control loop is reduced. Meta-analyses found that the bilateral medial frontal gyrus (MFG), left cingulate gyrus, left medial temporal gyrus, and fusiform gyrus all exhibited substantial activation in participants with IGD. Moreover, activations in the left MFG and the right cingulated gyrus were positively linked with the on-line time of IGD individuals (46, 47). The functional connectivity between the dorsolateral prefrontal cortex and the posterior cingulate cortex of IGAs was significantly lower than that of healthy subjects, and the degree of reduction was worse than that of the Stroop task performance (48, 49). Similar to heroin addiction, the decline in the functional connectivity of brain regions in the cognitive control circuit of IGAs will lead to their uncontrollable addictive behavior (50, 51).

ii. The functional connectivity between the cognitive control circuit and the memory-learning circuit is reduced. Sepede et al. found that the functional connectivity between the amygdala and the left dorsolateral prefrontal cortex was reduced in IGAs, and the lower the functional connectivity, the higher the impulsivity of addicts (52). This shows that IGAs cannot timely and effectively control the internet game-seeking motivation induced by the memory of addiction pleasure, and thus show higher impulsive internet game behavior.

It can be seen that although both IGAs and heroin addicts have impairments in cognitive and motivational functions, the underlying neural mechanisms may be different. In terms of cognitive impairment, the brain structure atrophy of heroin addicts mainly occurs in the relevant brain areas of the cognitive control circuit, and there is a wider range of brain functional connectivity abnormalities among the four circuits, while the brain structure atrophy of IGAs mainly occurred in the relevant brain areas of the memory-learning circuit, and the abnormal range of functional connectivity between the four circuit brain areas was also small. These differences indicate that there may be differences in the depth of cognitive impairment between the two addictions; that is, compared with IGAs, heroin addicts may have more advanced cognitive impairment. In terms of motivational function impairment, heroin addicts mainly show structural atrophy of the reward circuit and decreased functional

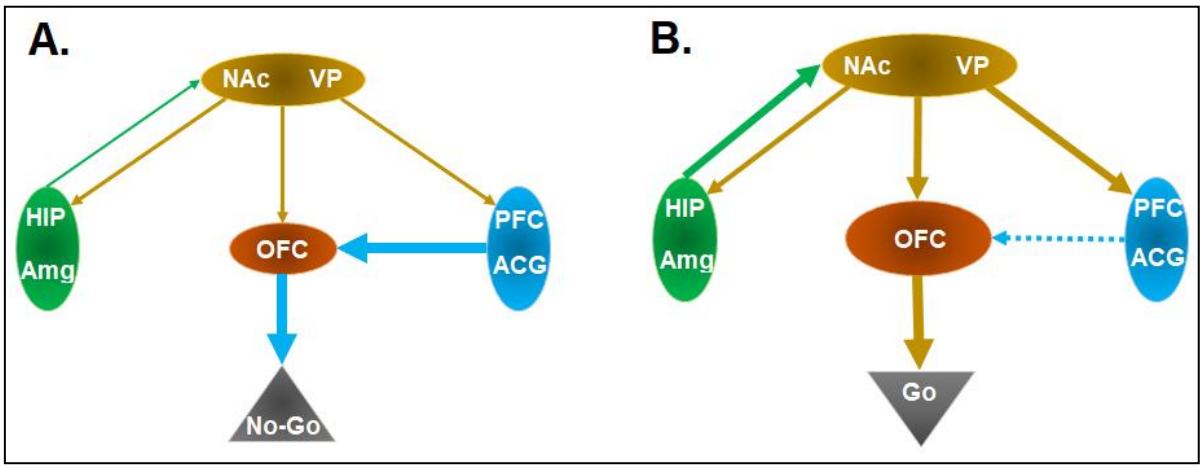

Figure 2. A Comparison of the Brain Circuits in a Healthy Brain and Those in an Addicted Brain.
Normally, the four circuits are in a state of equilibrium, with the OFC having the final control of the behavior, i.e., drug usage is prohibited. However, with addiction, this equilibrium is broken, and the drive to use drugs becomes stronger, drug memories become more dominant, and "top-down" mechanisms weaken to the point that drug usage is out of control that results in a "Go-and-Use" state.

connectivity of related brain regions, while IGAs mainly show structural atrophy of motivational circuit-related brain areas and related brain regions.

Impulse Control Dysfunction

Uncontrollable impulsive seeking of addictive behavior is a common psychological and behavioral feature of heroin and IGAs, and MRI studies have examined Go/No-Go task state impulse control ability and its neural mechanisms in these two types of addicts.

Heroin Addiction: The Activation Level of Some Brain Regions of the Cognitive Control Circuit is Reduced

Vassileva and colleagues found that heroin addicts showed higher impulsivity in the Go/No-Go experimental task, which was accompanied by decreased activation of cognitive control circuits (53). Using contextual Go/No-Go task, first the "Go" condition, which requires the subjects to press the upward arrow, and then the "Reverse" condition that requires the subjects to press the downward arrow. Behavioral results showed that only in the "Reverse" condition do heroin addicts have a shorter key press response time than healthy subjects, and the error rate is also high, showing an obvious impulse response bias, and simultaneous MRI results showed that the activation of the ACG was significantly lower in heroin addicts compared with comparisons (54).

Internet Game Addiction: The Activation Level of Some Brain Regions in the Cognitive Control Loop is Enhanced

The study of internet game addiction also found that they showed higher impulsivity in the Go/No-Go task, but the activation of cognitive control loops showed a significant increase. Casey et al. found that the activation of the left medial superior frontal gyrus, the right anterior cingulate gyrus, and the right superior/middle frontal gyrus were significantly enhanced when IGAs engaged in the Go/No-Go task (55). Ko et al. also found that IGAs with activation in the left orbitofrontal cortex was also significantly enhanced in addicts during the No-Go task (56). The results of these two studies indicate that when IGAs engage in No-Go tasks that require inhibitory control, although they mobilize high cognitive neural resources, they still cannot effectively control their own impulses, so their keystroke error rate is higher. Behavioral and MRI data show that when the background is images of internet games, although the error rate of IGAs is still high when engaging in the No-Go task, the activation degree of the right dorsolateral prefrontal cortex is significantly reduced, which shows that their cognitive control processing may have produced dependence on internet information (57).

These studies found a somewhat contradictory but interesting result, that is, under the task of stopping the dominant response, heroin addicts and IGAs showed opposite brain activation patterns: the activation level of the cognitive control loop of the former was weakened and that of the latter was enhanced. This is that when the impulsive response needs to be suppressed, both types of addicts need to enhance the activation of brain areas related to cognitive control circuits, but because the cognitive control circuits of heroin addicts appear to be damaged, but the degree of damage to the brain areas related to the cognitive control circuit of IGAs is relatively mild (**Figure 2**).

Conclusion

Although both IGAs and heroin addicts have some psychological and behavioral characteristics of addiction (abnormal cognitive and motivational function, stronger craving induced by addiction cues, cognitive decision-making biased towards reward and high risk, and impulse control disorders), the neural mechanisms found are similar and also different.

The similar points are: (i) In the resting state, some brain regions of the four addiction circuits and the functional connectivity between each other decreases, which can explain why the two types of addicts have abnormal cognitive and motivational functions; (ii) In the induced state, addiction relevant cues can induce strong and extensive activation of many brain regions of the four addiction circuits in addicts, which should be the neurological basis for the stronger craving induced by addiction-related cues in the two types of addicts. The different points are: (i) The location and scope of the brain regions with brain structure atrophy and functional connectivity reduction in the resting state are different, and the brain damage of heroin addicts tends to be in more advanced brain regions, mainly in the prefrontal cortex cognitive control loop, followed by the reward loop where the reward center is located, while the brain damage of IGAs tends to be in the lower brain areas, mainly in the memory-learning loop and motivation loop. This difference helps to explain why the addiction degree of heroin is deeper and the difficulty of quitting addiction is greater than that of many IGAs. When impulse control is lost, the corresponding nerve cells cannot be effectively activated to exert their control function, while IGAs can exert corresponding functions through compensatory enhanced activation in the same situation because the damage to these brain areas is relatively mild.

Based on the above comparison of the neural mechanisms underlying the four typical addiction characteristics of the two types of addicts, it can be tentatively believed that internet game addiction should be a psychotic disorder of the same nature as heroin addiction, but the possibility of recovery or self-healing after treatment is also greater. But at the same time, it should also be noted that this conclusion cannot be confirmed based on the results of existing MRI studies alone. In order to draw definite conclusions, further studies are needed.■

References

1. Camí J, Farré M. Drug addiction. N Engl J Med 2003; 349(10):975-986. DOI: https://doi.org/10.1056/NEJMra023160
2. Sussman CJ, Harper JM, Stahl JL, Weigle P. Internet and video game addictions: Diagnosis, epidemiology, and neurobiology. Child Adolesc Psychiatr Clin N Am 2018; 27(2):307-326. DOI: https://doi.org/10.1016/j.chc.2017.11.015
3. Alavi SS, Ferdosi M, Jannatifard F, Eslami M, Alaghemandan H, Setare M. Behavioral addiction versus substance addiction: Correspondence of psychiatric and psychological views. Int J Prev Med 2012; 3(4):290-294.
4. Alavi SS, Maracy MR, Jannatifard F, Eslami M. The effect of psychiatric symptoms on the internet addiction disorder in Isfahan's University students. J Res Med Sci 2011; 16(6):793-800.
5. Kuss DJ, Lopez-Fernandez O. Internet addiction and problematic Internet use: A systematic review of clinical research. World J Psychiatry 2016; 6(1):143-176. DOI: https://doi.org/10.5498/wjp.v6.i1.143
6. Petry NM, Zajac K, Ginley MK. Behavioral addictions as mental disorders: To be or not to be? Annu Rev Clin Psychol 2018; 14:399-423. DOI: https://doi.org/10.1146/annurev-clinpsy-032816-045120
7. Yau YH, Crowley MJ, Mayes LC, Potenza MN. Are Internet use and video-game-playing addictive behaviors? Biological, clinical and public health implications for youths and adults. Minerva Psichiatr 2012; 53(3):153-170.
8. Estévez A, Jáuregui P, Sánchez-Marcos I, López-González H, Griffiths MD. Attachment and emotion regulation in substance addictions and behavioral addictions. J Behav Addict 2017; 6(4):534-544. DOI: https://doi.org/10.1556/2006.6.2017.086
9. Koob GF, Volkow ND. Neurobiology of addiction: A neurocircuitry analysis. Lancet Psychiatry 2016; 3(8):760-773. DOI: https://doi.org/10.1016/S2215-0366(16)00104-8
10. Love T, Laier C, Brand M, Hatch L, Hajela R. Neuroscience of internet pornography addiction: A review and update. Behav Sci (Basel) 2015; 5(3):388-433. DOI: https://doi.org/10.3390/bs5030388
11. Tiffany ST, Wray JM. The clinical significance of drug craving. Ann N Y Acad Sci 2012; 1248:1-17. DOI: https://doi.org/10.1111/j.1749-6632.2011.06298.x
12. Substance Abuse and Mental Health Services Administration (US); Office of the Surgeon General (US). Facing Addiction in America: The Surgeon General's Report on Alcohol, Drugs, and Health [Internet]. Washington (DC): US Department of Health and Human Services; 2016 Nov. Chapter 2, The neurobiology of substance use, misuse, and addiction. Available at: https://www.ncbi.nlm.nih.gov/books/NBK424849/
13. Volkow ND, Koob GF, McLellan AT. Neurobiologic advances from the brain disease model of addiction. N Engl J Med 2016; 374(4):363-371. DOI: https://doi.org/10.1056/NEJMra1511480
14. Månsson V, Andrade J, Jayaram-Lindström N, Berman AH. "I see myself": Craving imagery among in-

dividuals with addictive disorders. J Addict Dis 2023; 41(1):64-77. DOI: https://doi.org/10.1080/10550887.2022.2058299

15. NIDA. Drugs and the Brain. National Institute on Drug Abuse website. March 22, 2022. Last Access: March 07, 2023. Available at: https://nida.nih.gov/publications/drugs-brains-behavior-science-addiction/drugs-brain
16. Li Q, Wang Y, Zhang Y, Li W, Zhu J, Zheng Y, Chen J, Zhao L, Zhou Z, Liu Y, Wang W, Tian J. Assessing cue-induced brain response as a function of abstinence duration in heroin-dependent individuals: An event-related fMRI study. PLoS One 2013; 8(5):e62911. DOI: https://doi.org/10.1371/journal.pone.0062911
17. Wei X, Li Q, Chen J, Shen B, Wang W, Li W. Differences in cue-induced brain activation between long-term methadone maintenance treatment and protracted abstinence in heroin use disorder patients: A functional magnetic resonance imaging study. Quant Imaging Med Surg 2021; 11(5):2104-2113. DOI: https://doi.org/10.21037/qims-20-1002
18. Liu GC, Yen JY, Chen CY, Yen CF, Chen CS, Lin WC, Ko CH. Brain activation for response inhibition under gaming cue distraction in internet gaming disorder. Kaohsiung J Med Sci 2014; 30(1):43-51. DOI: https://doi.org/10.1016/j.kjms.2013.08.005
19. Sun Y, Sun J, Zhou Y, Ding W, Chen X, Zhuang Z, Xu J, Du Y. Assessment of in vivo microstructure alterations in gray matter using DKI in Internet gaming addiction. Behav Brain Funct 2014; 10:37. DOI: https://doi.org/10.1186/1744-9081-10-37
20. Anderson BA. What is abnormal about addiction-related attentional biases? Drug Alcohol Depend 2016; 167:8-14. DOI: https://doi.org/10.1016/j.drugalcdep.2016.08.002
21. Wiehler A, Peters J. Reward-based decision making in pathological gambling: the roles of risk and delay. Neurosci Res 2015; 90:3-14. DOI: https://doi.org/10.1016/j.neures.2014.09.008
22. Gorzelańczyk EJ, Walecki P, Błaszczyszyn M, Laskowska E, Kawala-Sterniuk A. Evaluation of risk behavior in gambling addicted and opioid addicted individuals. Front Neurosci 2021; 14:597524. DOI: https://doi.org/10.3389/fnins.2020.597524
23. Goudriaan AE, Yücel M, van Holst RJ. Getting a grip on problem gambling: What can neuroscience tell us? Front Behav Neurosci 2014; 8:141. DOI: https://doi.org/10.3389/fnbeh.2014.00141
24. Schmidt A, Walter M, Gerber H, Schmid O, Smieskova R, Bendfeldt K, Wiesbeck GA, Riecher-Rössler A, Lang UE, Rubia K, McGuire P, Borgwardt S. Inferior frontal cortex modulation with an acute dose of heroin during cognitive control. Neuropsychopharmacology 2013; 38(11):2231-2239. DOI: https://doi.org/10.1038/npp.2013.123
25. Goldstein RZ, Volkow ND. Dysfunction of the prefrontal cortex in addiction: Neuroimaging findings and clinical implications. Nat Rev Neurosci 2011; 12(11):652-669. DOI: https://doi.org/10.1038/nrn3119
26. Kuss DJ, Griffiths MD. Internet and gaming addiction: A systematic literature review of neuroimaging studies. Brain Sci 2012; 2(3):347-374. DOI: https://doi.org/10.3390/brainsci2030347
27. Cho TH, Nah Y, Park SH, Han S. Prefrontal cortical activation in Internet Gaming Disorder Scale high scorers during actual real-time internet gaming: A preliminary study using fNIRS. J Behav Addict 2022; 11(2):492-505. DOI: https://doi.org/10.1556/2006.2022.00017
28. Dong G, Li H, Wang L, Potenza MN. Cognitive control and reward/loss processing in Internet gaming disorder: Results from a comparison with recreational Internet game-users. Eur Psychiatry 2017; 44:30-38. DOI: https://doi.org/10.1016/j.eurpsy.2017.03.004
29. Weinstein A, Lejoyeux M. Neurobiological mechanisms underlying internet gaming disorder. Dialogues Clin Neurosci 2020; 22(2):113-126. DOI: https://doi.org/10.31887/DCNS.2020.22.2/aweinstein
30. Dong G, Potenza MN. A cognitive-behavioral model of Internet gaming disorder: Theoretical underpinnings and clinical implications. J Psychiatr Res 2014; 58:7-11. DOI: https://doi.org/10.1016/j.jpsychires.2014.07.005
31. Denier N, Schmidt A, Gerber H, Schmid O, Riecher-Rössler A, Wiesbeck GA, Huber CG, Lang UE, Radue EW, Walter M, Borgwardt S. Association of frontal gray matter volume and cerebral perfusion in heroin addiction: A multimodal neuroimaging study. Front Psychiatry 2013; 4:135. DOI: https://doi.org/10.3389/fpsyt.2013.00135
32. Shi H, Liang Z, Chen J, Li W, Zhu J, Li Y, Ye J, Zhang J, Xue J, Liu W, Wang F, Wang W, Li Q, He X. Gray matter alteration in heroin-dependent men: An atlas-based magnetic resonance imaging study. Psychiatry Res Neuroimaging 2020; 304:111150. DOI: https://doi.org/10.1016/j.pscychresns.2020.111150
33. Stewart JL, May AC, Paulus MP. Bouncing back: Brain rehabilitation amid opioid and stimulant epidemics. Neuroimage Clin 2019; 24:102068. DOI: https://doi.org/10.1016/j.nicl.2019.102068
34. Ceceli AO, Huang Y, Kronberg G, Malaker P, Miller P, King S, Gaudreault PO, McClain N, Gabay L, Vasa D, Newcorn JH, Ekin D, Alia-Klein N, Goldstein RZ. Common and distinct fronto-striatal volumetric changes in heroin and cocaine use disorders. Brain 2022; 2022:awac366. DOI: https://doi.org/10.1093/brain/awac366
35. Gordon HW. Differential activation of the left and right cerebral hemispheres of individuals who use or are dependent on drugs of abuse. J Drug Abuse 2018; 4(2):10. DOI: https://doi.org/10.21767/2471-853X.100077
36. Motzkin JC, Baskin-Sommers A, Newman JP, Kiehl KA, Koenigs M. Neural correlates of substance abuse: Reduced functional connectivity between areas underlying reward and cognitive control. Hum Brain Mapp 2014; 35(9):4282-4292. DOI: https://doi.org/10.1002/hbm.22474
37. Schmidt A, Walter M, Gerber H, Seifritz E, Brenneisen R, Wiesbeck GA, Riecher-Rössler A, Lang UE, Borgwardt S. Normalizing effect of heroin maintenance treatment on stress-induced brain connectivity. Brain 2015; 138(Pt 1):217-228. DOI:

https://doi.org/10.1093/brain/awu326

38. Lin HC, Wang PW, Wu HC, Ko CH, Yang YH, Yen CF. Altered gray matter volume and disrupted functional connectivity of dorsolateral prefrontal cortex in men with heroin dependence. Psychiatry Clin Neurosci. 2018; 72(6):435-444. DOI: https://doi.org/10.1111/pcn.12655
39. Ma N, Liu Y, Li N, Wang CX, Zhang H, Jiang XF, Xu HS, Fu XM, Hu X, Zhang DR. Addiction related alteration in resting-state brain connectivity. Neuroimage 2010; 49(1):738-744. DOI: https://doi.org/10.1016/j.neuroimage.2009.08.037
40. Wang W, Wang YR, Qin W, Yuan K, Tian J, Li Q, Yang LY, Lu L, Guo YM. Changes in functional connectivity of ventral anterior cingulate cortex in heroin abusers. Chin Med J (Engl) 2010; 123(12):1582-1588.
41. Zhai TY, Shao YC, Xie CM, Ye EM, Zou F, Fu LP, Li WJ, Chen G, Chen GY, Zhang ZG, Li SJ, Yang Z. Altered intrinsic hippocmapus declarative memory network and its association with impulsivity in abstinent heroin dependent subjects. Behav Brain Res 2014; 272:209-217. DOI: https://doi.org/10.1016/j.bbr.2014.06.054
42. Lin X, Dong G, Wang Q, Du X. Abnormal gray matter and white matter volume in 'Internet gaming addicts'. Addict Behav 2015; 40:137-143. DOI: https://doi.org/10.1016/j.addbeh.2014.09.010
43. Ko CH, Hsieh TJ, Wang PW, Lin WC, Yen CF, Chen CS, Yen JY. Altered gray matter density and disrupted functional connectivity of the amygdala in adults with Internet gaming disorder. Prog Neuropsychopharmacol Biol Psychiatry 2015; 57:185-192. DOI: https://doi.org/10.1016/j.pnpbp.2014.11.003
44. Brand M, Young KS, Laier C. Prefrontal control and internet addiction: A theoretical model and review of neuropsychological and neuroimaging findings. Front Hum Neurosci 2014; 8:375. DOI: https://doi.org/10.3389/fnhum.2014.00375
45. Lin F, Zhou Y, Du Y, Qin L, Zhao Z, Xu J, Lei H. Abnormal white matter integrity in adolescents with internet addiction disorder: A tract-based spatial statistics study. PLoS One 2012; 7(1):e30253. DOI: https://doi.org/10.1371/journal.pone.0030253
46. Meng Y, Deng W, Wang H, Guo W, Li T. The prefrontal dysfunction in individuals with Internet gaming disorder: A meta-analysis of functional magnetic resonance imaging studies. Addict Biol 2015; 20(4):799-808. DOI: https://doi.org/10.1111/adb.12154
47. Solly JE, Hook RW, Grant JE, Cortese S, Chamberlain SR. Structural gray matter differences in problematic usage of the internet: A systematic review and meta-analysis. Mol Psychiatry 2022; 27(2):1000-1009. DOI: https://doi.org/10.1038/s41380-021-01315-7
48. Li W, Li Y, Yang W, Zhang Q, Wei D, Li W, Hitchman G, Qiu J. Brain structures and functional connectivity associated with individual differences in Internet tendency in healthy young adults. Neuropsychologia 2015; 70:134-144. DOI: https://doi.org/10.1016/j.neuropsychologia.2015.02.019
49. Sun JT, Hu B, Chen TQ, Chen ZH, Shang YX, Li YT, Wang R, Wang W. Internet addiction-induced brain structure and function alterations: A systematic review and meta-analysis of voxel-based morphometry and resting-state functional connectivity studies. Brain Imaging Behav 2023; In press. DOI: https://doi.org/10.1007/s11682-023-00762-w
50. Chen H, Dong G, Li K. Overview on brain function enhancement of Internet addicts through exercise intervention: Based on reward-execution-decision cycle. Front Psychiatry 2023; 14:1094583. DOI: https://doi.org/10.3389/fpsyt.2023.1094583
51. Darnai G, Perlaki G, Zsidó AN, Inhóf O, Orsi G, Horváth R, Nagy SA, Lábadi B, Tényi D, Kovács N, Dóczi T, Demetrovics Z, Janszky J. Internet addiction and functional brain networks: Task-related fMRI study. Sci Rep 2019; 9(1):15777. DOI: https://doi.org/10.1038/s41598-019-52296-1
52. Sepede G, Tavino M, Santacroce R, Fiori F, Salerno RM, Di Giannantonio M. Functional magnetic resonance imaging of internet addiction in young adults. World J Radiol 2016; 8(2):210-225. DOI: https://doi.org/10.4329/wjr.v8.i2.210
53. Vassileva J, Paxton J, Moeller FG, Wilson MJ, Bozgunov K, Martin EM, Gonzalez R, Vasilev G. Heroin and amphetamine users display opposite relationships between trait and neurobehavioral dimensions of impulsivity. Addict Behav 2014; 39(3):652-659. DOI: https://doi.org/10.1016/j.addbeh.2013.11.020
54. Dousset C, Chenut C, Kajosch H, Kornreich C, Campanella S. Comparison of neural correlates of reactive inhibition in cocaine, heroin, and polydrug users through a contextual Go/No-Go task using event-related potentials. Biology (Basel) 2022; 11(7):1029. DOI: https://doi.org/10.3390/biology11071029
55. Casey BJ, Trainor RJ, Orendi JL, Schubert AB, Nystrom LE, Giedd JN, Castellanos FX, Haxby JV, Noll DC, Cohen JD, Forman SD, Dahl RE, Rapoport JL. A developmental functional mri study of prefrontal activation during performance of a Go-No-Go task. J Cogn Neurosci 1997; 9(6):835-847. DOI: https://doi.org/10.1162/jocn.1997.9.6.835
56. Ko CH, Chen SH, Wang CH, Tsai WX, Yen JY. The clinical utility of the Chen Internet Addiction Scale-Gaming Version, for internet gaming disorder in the DSM-5 among young adults. Int J Environ Res Public Health 2019; 16(21):4141. DOI: https://doi.org/10.3390/ijerph16214141
57. Ding WN, Sun JH, Sun YW, Zhou Y, Li L, Xu JR, Du YS. Altered default network resting-state functional connectivity in adolescents with Internet gaming addiction. PLoS One 2013; 8(3):e59902. DOI: https://doi.org/10.1371/journal.pone.0059902

Received: January 15, 2023 | Revised: February 10, 2023 | Accepted: February 22, 2023