Structural and Functional Characteristics of Impulsivity-Related Brain Regions in Long-Term Abstinent Heroin Addicts

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Date: 2021-03-26T00:00:00+00:00

Abstract

Impulsivity is a hallmark characteristic of drug addiction, encompassing both inhibitory control over drug use and motivational components that drive drug-seeking behavior; an imbalance between these systems leads to impulsive drug use. Heroin addicts exhibit inherent impulsive personality traits, and prolonged heroin use induces abnormalities in brain structure and function associated with impulsivity. Currently, it remains unclear whether impulsivity and related brain structural and functional alterations persist following abstinence. This study employed voxel-based morphometry, amplitude of low-frequency fluctuation (ALFF), regional homogeneity (ReHo), and functional connectivity analyses in 35 heroin abstainers and 26 healthy controls without addiction history to investigate the structural and functional status of driver and control brain networks related to impulsivity after long-term abstinence. The results demonstrated that, compared with controls, the abstinence group showed significantly reduced total gray matter volume and gray matter volume in the right medial superior frontal gyrus, with gray matter volume in the right middle temporal gyrus and left medial paracingulate gyrus decreasing as a function of total drug dosage; functional connectivity between the right orbital inferior frontal gyrus and caudate nucleus was significantly enhanced, while connectivity between the right middle temporal gyrus and left precentral gyrus was significantly reduced; ReHo values in the right orbital middle frontal gyrus and ALFF values in the right orbital inferior frontal gyrus and left hippocampus were significantly lower than controls, whereas ReHo values in the right postcentral gyrus were significantly higher. These brain regions' status aligns with the neural basis of impulsivity, indicating that after 44 months of abstinence, heroin abstainers still exhibit abnormalities in reward, salience, and habitual behavior network systems, which correlate with total addictive drug usage. These abnormalities

may represent the neural substrate underlying the driving force of addictive impulsivity and could serve as a factor explaining relapse vulnerability following abstinence.

Full Text

Structural and Functional Characteristics of Impulsivity-Related Brain Regions in Heroin Addicts with Long-Term Abstinence

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Abstract

Impulsivity is a hallmark characteristic of drug addiction, encompassing both inhibitory control mechanisms that suppress drug use and motivational drives that promote drug-seeking behavior. Imbalance between these systems leads to impulsive drug-taking behavior. Heroin addicts exhibit impulsive personality traits, and prolonged heroin use causes abnormalities in brain structure and function related to impulsivity. However, it remains unclear whether these structural and functional abnormalities persist after withdrawal. This study employed voxel-based morphometry (VBM), amplitude of low-frequency fluctuation (ALFF), regional homogeneity (ReHo), and functional connectivity analyses to investigate the structural and functional status of brain networks associated with impulsive drive and control systems in 35 heroin abstainers compared with 26 healthy controls without any addiction history. Results showed that compared to controls, the abstinent group exhibited significantly reduced total gray matter volume and gray matter volume in the right medial superior frontal gyrus. Gray matter volume in the right middle temporal gyrus and left medial paracingulate gyrus decreased with increasing cumulative heroin dose. Functional connectivity was significantly enhanced between the right orbital inferior frontal gyrus and caudate nucleus, while connectivity between the right middle temporal gyrus and left precentral gyrus was significantly reduced. ReHo values in the right orbital middle frontal gyrus and ALFF values in the right orbital inferior frontal gyrus and left hippocampus were significantly lower than controls, whereas ReHo values in the right postcentral gyrus were significantly higher. These brain regions align with the neural substrates of impulsivity, indicating that even after 44 months of abstinence, heroin abstainers still show abnormal-

ities in reward, salience, and habitual behavior networks, which correlate with total drug consumption. These abnormalities may constitute the neural basis of addictive impulsivity as a driving force and represent one factor explaining relapse vulnerability after withdrawal.

Keywords: Heroin addiction, Voxel-based morphometry, Amplitude of low-frequency fluctuation, Regional homogeneity, Resting-state functional connectivity

Impulsivity is defined as "actions or spontaneous, unconscious behavioral habits that lack sufficient forethought, are overly risky, reckless, context-inappropriate, and disregard consequences, leading to undesirable outcomes"(Pattij & De Vries, 2013). It is a critical factor in substance addiction (Everitt & Robbins, 2016), with high impulsivity predicting the transition from casual drug use to compulsive behavior (Belin et al., 2008). Impulsivity can be divided into trait impulsivity and state impulsivity. The former is considered determined by neurophysiological characteristics. Most addicts possess impulsive personality traits that are reportedly associated with familial heredity, exist prior to drug use, and manifest as abnormalities in brain structure and function.

Trait impulsivity existing before cocaine use has been found to correlate with structural abnormalities in the prefrontal-striatal pathway (Ersche et al., 2013), which is associated with behavioral inhibitory control. Moreover, addicts' siblings who have never used cocaine show similar brain activation patterns and gray matter volume changes (Ersche et al., 2012; Ersche et al., 2010; Morein-Zamir & Robbins, 2015). These activation and structural characteristics suggest that early drug abuse and impulsivity at this stage are associated with prefrontal and nucleus accumbens-related control functions—that is, impulsive personality traits (Everitt & Robbins, 2016).

This evidence reflects personality trait problems that exist before substance abuse. Such traits are based on abnormal neural mechanisms that confer inherently weak inhibitory capacity, making individuals more vulnerable to developing drug use behaviors and subsequent addiction. Prospective studies in human infancy also demonstrate that behavioral impulsivity and accompanying brain function exist at least partially prior to drug use, constituting a risk factor. Thus, trait impulsivity can be inferred as a susceptibility marker for substance addiction (Everitt & Robbins, 2013), with its biological basis being familial heredity-related endophenotypic characteristics—specifically, functional and structural abnormalities in the ventral striatum-medial prefrontal cortex (VS-mPFC) circuit—that lead to reduced top-down control, thereby increasing impulsivity and drug abuse risk.

However, although trait impulsivity and its neural basis contribute to reduced inhibitory control function as vulnerability factors in substance use, these brain structural associations are also observed in non-addicted individuals (Deserno et al., 2015). This suggests that the abnormal neuroanatomical structures and activation patterns observed in addicts may not be the sole cause of addiction.

The biological basis of inhibitory control-related trait impulsivity may only play an origination or moderating role in addictive behavior, with other factors contributing to uncontrollable impulsive drug use in later stages.

Long-term drug use and genetic factors lead addicts to exhibit two types of state impulsivity: response inhibition (motor impulsivity) and risky decision-making (waiting impulsivity, cognitive control problems), manifesting as damage to the dorsolateral prefrontal cortex (dlPFC) and dorsomedial prefrontal cortex (dmPFC) (Zilverstand et al., 2018). Research shows that impulsivity in addicts is closely related to abnormal activation in frontal regions, particularly reduced baseline glucose metabolism in the prefrontal cortex (including dlPFC, anterior cingulate cortex, and medial orbital frontal cortex) and low levels of striatal dopamine D2 receptors (Koob & Volkow, 2010, 2016).

Trait and state impulsivity interact, making addicts more likely to try addictive substances and difficult to control both "goal-directed" drug use behaviors triggered by drug effects in early use stages and automated habitual behaviors after addiction. During successful completion of inhibition tasks, significant activation of dlPFC in adolescent substance users can predict fewer problem behaviors, suggesting that dlPFC function plays an important role in response inhibition (Martz et al., 2018). That is, dlPFC can modulate habitual drug use behaviors formed through long-term use; when its function is impaired, it becomes difficult to control the expression of habitual behaviors, manifesting as strong stopping impulsivity.

The iRISA (Impaired Response Inhibition and Salience Attribution) model posits that impaired response inhibition and salience attribution in brain regions constitute the primary cause of addictive impulsivity, manifested as drug-seeking and use under relevant cues (Goldstein & Volkow, 2002). Response inhibition is a control force that, as mentioned above, is already manifested in personality traits and further damaged during drug use. Salience, conversely, is a driving force that promotes drug use behavior; without sufficient control, drug use behavior cannot be prevented. Studies of alcohol, cocaine, and codeine addiction have all found abnormal connectivity in salience networks (McHugh et al., 2015; Qiu et al., 2017; Zhu et al., 2017). However, the driving forces behind addictive impulsivity clearly extend beyond salience. Evidence shows that reward, habitual behavior, addiction memory, and executive function brain regions all play corresponding roles in addiction (Zilverstand et al., 2018), serving as control and drive systems respectively.

In initial drug use, addicts are driven by drug reward effects to continue use. The "reward" effect is regulated by mechanisms integrated by the nucleus accumbens and its peri-limbic subregions, such as the limbic cortical system. This region' s involvement enhances drug reward evaluation and anticipation, exacerbating the urgency of drug use (Dalley & Robbins, 2017). It drives relapse during early drug use, strong craving without drug availability (Zeng et al., 2018), and withdrawal states (Koob & Volkow, 2016). Cocaine addiction research has found that imbalance between reward and executive control circuits

affects impulsive drug use, showing abnormal functional connectivity in brain cortex regions related to executive control (Ray et al., 2015). Moreover, hyperactivation and hyperconnectivity in reward circuits, at the expense of connectivity outside this network, characterize cocaine addiction (Vaquero et al., 2017). Cocaine users also show abnormal associations between reward-executive control network coupling and impulsive decision-making (Hobkirk et al., 2019). Heroin addicts show stronger coupling between midbrain and ventromedial prefrontal cortex but weaker coupling between midbrain and dorsolateral prefrontal cortex —that is, dysregulation of the mesolimbic-prefrontal pathway in the reward system (Cheng et al., 2015). These abnormal connections in reward brain regions demonstrate that reward effects play an important role in impulsive behavior.

Additionally, "S-R" responses under relevant cues serve as a source of driving force. During drug use, conditioning establishes associations between drug-related cues and drug effects, transforming "goal-directed" behaviors controlled by reward effects into "stimulus-response (S-R)" habitual drug use behaviors. This S-R force also drives addictive impulsive behavior. Drug-related objects, negative emotions, and stress become important stimuli for drug use during long-term use, forming drug-related cues (conditioned stimuli) that trigger habitual drug use behaviors when presented (Wang et al., 2019). Abnormal connectivity between dorsal striatum (DS) and related motor brain regions constitutes the neural basis of this behavioral response (Everitt et al., 2016; Zeng et al., 2018), specifically manifested as altered sensorimotor control pathways in addicts that positively correlate with low fronto-striatal connectivity in the motor system (Lench et al., 2017). During negative emotional experiences, functional coupling between dlPFC and emotion-related regions increases, while functional connectivity between right inferior frontal gyrus and amygdala decreases during inhibition (Albein-Urios et al., 2014), indicating that relevant cues directly trigger dorsolateral striatum and motor brain regions to form S-R responses. This response manifests as habitual drug use reactions and craving-induced compulsive drug use behavior—important features of addiction and key manifestations of addictive impulsivity.

Thus, reward and S-R habitual behaviors formed through conditioning become sources of impulsive drive, while inhibitory and cognitive control damage caused by innate factors and long-term drug use results in low control capacity in addicts. When reward and S-R forces are sufficiently strong and inhibitory control is weak, their interaction leads to uncontrollable habitual and compulsive drug-seeking and use behaviors (Zeng et al., 2018; Zeng et al., 2015), creating impulsivity and the observable phenomenon of continuous drug use and relapse.

However, if the neural network functions driving drug use could gradually recover with prolonged abstinence, then even if inhibitory control remains low (determined by impulsive personality traits) or potentially improves with abstinence (state impulsivity), addicts might still resist weakened reward or S-R drive forces, thereby reducing impulsive drug use. That is, as abstinence duration increases, either the drive forces affecting addictive impulsivity weaken or control

capacity improves, potentially enabling abstainers to maintain abstinence and prevent relapse despite unchangeable impulsive personality traits.

Previous studies show varying brain structural and functional outcomes after withdrawal, related to different brain regions and their functions, heroin dosage, addiction duration, and abstinence length. Within 6 months of abstinence, brain gray matter density increases (He et al., 2008); after 6 months, white matter integrity recovers (Shen et al., 2012; Yan et al., 2016), but working memory shows no significant recovery and response inhibition function remains impaired (Fu et al., 2008), with lower gray matter density in anterior cingulate cortex and putamen (Keihani et al., 2017) and persistent damage in white matter of reward and cognitive control brain regions and executive function (Yan et al., 2015; Yang et al., 2019). With longer abstinence, emotional processing capacity in 18-month abstainers and reward cognitive function in 3-year abstainers show some recovery (Zhou et al., 2014a; Zhou et al., 2014b). However, human PET studies indicate that even after long-term detoxification, ventral striatal dopamine D2 receptors remain reduced (Dalley et al., 2007).

These studies have focused primarily on volume changes in impulsive control brain regions, with less research on connectivity changes in different brain regions resulting from incentive factors related to driving forces. Therefore, this study employed regional homogeneity (ReHo) and amplitude of low-frequency fluctuation (ALFF) analyses, combined with voxel-based morphometry (VBM) and resting-state functional connectivity (rsFC) analysis, to investigate the structural and functional status of brain networks related to impulsive drive and control systems in heroin abstainers after long-term withdrawal, starting from the behavioral characteristics and neural mechanisms of addiction. This approach aims to further understand factors influencing relapse after withdrawal and provide theoretical guidance for clinical intervention and treatment. We hypothesized that even without cues, heroin abstainers would show abnormal functional connectivity in drive-related reward systems such as ventral striatum and brain regions forming cue-habituation based on reward learning, including dorsal striatum responsible for automated behaviors and motor brain regions. Limbic systems related to emotion might also show connectivity with brain regions related to automated behavior. Meanwhile, connectivity between prefrontal cortex closely related to control and automated behavior brain regions would also be abnormal. Additionally, these brain regions might undergo structural changes.

2.1 Participants

Addicted participants were recruited on-site at a voluntary drug rehabilitation center in Guangdong Province and a methadone treatment clinic at Guangzhou Brain Hospital. A total of 35 heroin abstainers and 26 healthy controls participated, aged 29-52 years, right-handed, with no color blindness or weakness. Inclusion criteria for the abstinent group were: (1) heroin as primary substance of addiction; (2) meeting DSM-V criteria for substance use disorder with no

other psychiatric disorders; (3) no claustrophobia; (4) negative urine test for heroin and other addictive substances. Control participants were primarily support staff recruited through written advertisements from a Guangzhou hospital, with inclusion criteria: (1) healthy; (2) no metal implants; (3) no tumors or serious injuries; (4) no claustrophobia or psychiatric disorders. The study was reviewed and approved by the Ethics Committee of the School of Psychology at South China Normal University. All participants understood the study' s purpose, content, methods, and potential risks, signed informed consent before the experiment, and received 120 RMB compensation after completion.

2.2 Data Acquisition

MRI data were acquired using a 3T Siemens Trio system. T2*-weighted echo-planar imaging (EPI) sequences were collected to measure blood oxygen level-dependent (BOLD) signals, with 36 whole-brain axial images acquired per TR (thickness/gap = 3/0.7 mm, matrix size = 64 × 64, TR = 2200 ms, TE = 30 ms, flip angle = 90°, FOV = 200 × 200 mm^2). At the end of each session, high-resolution anatomical images were acquired using a standard T1-weighted 3D MPRAGE sequence for spatial preprocessing of EPI data (voxel size 1$×1×1mm^{3}$, thickness = 1 mm, TR = 2300 ms, TE = 3.24 ms, FA = 9°, FOV = 256 × 256 mm^2, matrix size = 256 × 256).

2.3 Data Processing and Statistics

This study first performed voxel-based morphometry, conducting two-sample t-tests ($p<0.05$) on total gray matter volume, total white matter volume, total cerebrospinal fluid volume, brain volume, total intracranial volume, and brain parenchyma ratio between groups. Whole-brain regional homogeneity and low-frequency amplitude analyses were then conducted. Based on ALFF results, the right orbital inferior frontal gyrus (15, 60, -6) was selected as the region of interest for functional connectivity analysis. All significantly activated brain regions were correlated with abstinence duration, drug use duration, and total drug dose, but only significant correlations are reported.

VBM data preprocessing was performed using the VBM8 toolbox in SPM 8 (http://www.fil.ion.ucl.ac.uk/spm/), including: (1) data format conversion from DICOM to NIFTI using dcm2niigui software; (2) quality inspection using MRIcron, excluding 3 subjects with non-standard data; (3) tissue segmentation of T1-weighted images into gray matter, white matter, and cerebrospinal fluid; (4) DARTEL iterative processing for gray matter, white matter, and cerebrospinal fluid; (5) spatial normalization to standard MNI space; (6) secondary quality inspection using SPM' s Check Reg function to exclude non-standard data; (7) smoothing with a 6mm full width at half maximum (FWHM) Gaussian kernel.

SPSS Statistics 22.0 was used for two-sample t-tests ($p<0.05$) on total gray matter volume, white matter volume, cerebrospinal fluid volume, brain volume, total intracranial volume, and brain parenchyma ratio. RESTplus1.21 (Jia et al.,

2019) was used for AlphaSim multiple comparison correction (corrected p<0.01), with age, sex, and education as covariates. Correlation analysis between gray matter volume and total heroin dose in the abstinent group was performed with an uncorrected threshold of p<0.001 and AlphaSim correction (corrected p<0.01). Significantly activated brain regions were selected as regions of interest (ROI), and gray matter volume in ROIs was correlated with total dose at p<0.05 significance level.

Regional homogeneity data preprocessing was performed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/) on MATLAB R2014a platform: (1) slice timing correction; (2) realignment for head motion correction and parameter generation; (3) co-registration of each subject' s EPI image to their T1 image using Dartel and transformation to standard brain space (resampled to 3$×3×$3 mm voxels); (4) removal of head motion signals and white matter/cerebrospinal fluid signals using Friston' s method; (5) extraction of low-frequency signals (0.01-0.08 Hz); (6) calculation of ReHo and ALFF values followed by smoothing with a 6mm FWHM Gaussian kernel.

Two-sample t-tests were performed on ReHo and ALFF Z-scores. Uncorrected thresholds were set at p<0.001, with AlphaSim multiple comparison correction using RESTplus1.21 (corrected p<0.01). Sex, age, and education were included as covariates to remove confounding effects.

Based on ALFF results, the right orbital inferior frontal gyrus (15, 60, -6) was selected as ROI with a 5mm radius. RESTplus1.21 was used for functional connectivity calculation and AlphaSim multiple comparison correction, with sex, age, and education as covariates.

3.1 Demographic Information

Sixty-four participants were enrolled. Two subjects with abnormal brain structure and one with enlarged ventricles were excluded for not meeting data processing standards, leaving 61 subjects for analysis. The heroin abstinent group (HAG) comprised 35 subjects (28 males, 80%), aged 34-49 years (40.69$±$3.61). Twelve subjects received standardized methadone maintenance treatment (10ml oral methadone daily) without other medications. The healthy control group (HCG) comprised 26 subjects (26 males, 100%). No statistically significant differences in basic information or brain metrics were found between complete abstainers and methadone-maintained abstainers (see Table 1). Therefore, this study did not distinguish between the two abstinence types and directly compared the combined abstinent group with healthy controls. Basic information comparison between groups is detailed in Table 2 .

Table 1 Basic information and brain metrics for complete abstinence and methadone maintenance groups (M±SD)

Measure	Complete Abstinence (n=23)	Methadone Maintenance (n=12)	Cohen' s d
Age (years)	40.20$±3.54|41.82±3.69|||*Education(years)*|9.04±1.4|9.45±1.04|||*Cigarettes/day*|12.99±5.42|15.48 *withdrawalheroin/day(g)*|0.55±0.28|0.65±0.27|||*Pre− withdrawalheroin/month(g)*|16.34±8.31|18.75±8.10|||*Useduration(months)*|200.76±40.84|223.80±		

Table 2 Basic information for heroin abstinent and control groups (M±SD)

Measure	Abstinent Group (n=35)	Control Group (n=26)	Cohen' s d
Age (years)	40.69$±3.61|42.31±8.45|||*Education(years)*|9.17±1.30|10.50±1.55|||*Cigarettes/day*|13.81±8.27|1 *withdrawalheroin/day(g)*|0.57±0.27|− |||*Pre − withdrawalheroin/month(g)*|17.03±8.21|− |||*Useduration(months)*|207.34±45.65|− |||*Totaldose(g)*|3614.67±2095.69|− |||*Abstinenceduration(months)*|43.55±$6.59		

3.2 Abnormal Brain Metrics in Heroin Abstinent Group

The heroin abstinent group showed significantly different total gray matter volume compared to healthy controls (p=0.03). See Table 3 .

Table 3 Two-sample t-test results for brain metrics between abstinent and control groups

Measure	Abstinent Group (n=35)	Control Group (n=26)	Cohen' s d
Total gray matter (mm^3)	625.41$±36.41\|654.26±63.43\|\|\|*Totalwhitematter*($mm^{\{3\})}$\|523.02±51.08\|540.36±9.03\|\|\|*TotalCSF*(mm {3})|2		

VBM results showed that under pAlphaSim<0.01, the heroin abstinent group had significantly reduced gray matter volume in the right medial superior frontal gyrus compared to healthy controls (see Table 4 , Figure 1 [Figure 1: see original paper]).

Table 4 Two-sample t-test for abnormal gray matter volume regions in abstinent group vs. controls

Region	Cluster size	MNI coordinates	pAlphaSim correction
Medial superior frontal gyrus (HAG<HCG)			<0.01

3.3 Correlation Between Total Heroin Dose and Gray Matter Volume in Abstinent Group

Correlation analysis between gray matter volume and abstinence duration, use duration, and total dose showed that gray matter volume in the right middle temporal gyrus and left medial paracingulate gyrus decreased significantly with increasing total heroin dose (see Table 5). Right middle temporal gyrus (56, -59, -5) and left medial paracingulate gyrus (-8, -38, -33) showed significant negative correlations with total dose (r=-0.56, p<0.001, see Figure 2 [Figure 2: see original paper]; r=-0.35, p<0.005, see Figure 3 [Figure 3: see original paper]). Correlations between use duration, abstinence duration and gray matter volume in these regions were not statistically significant.

Table 5 Brain regions where gray matter volume correlates with total dose in HAG

Region	Cluster size	MNI coordinates	pAlphaSim correction
Medial and paracingulate gyrus			<0.01

3.4 Differences in Regional Homogeneity and Low-Frequency Amplitude Between Abstinent and Control Groups

Under pAlphaSim<0.01, HAG showed significantly lower ReHo values in the right orbital middle frontal gyrus and significantly higher ReHo values in the right postcentral gyrus compared to controls (see Table 6 , Figure 4 [Figure 4: see original paper], Figure 5 [Figure 5: see original paper]).

Correlation between abnormal ReHo values and total dose showed no significant correlations for right orbital middle frontal gyrus (r=0.08, p=0.64) or right postcentral gyrus (r=0.13, p=0.48).

Table 6 Two-sample t-test for regional homogeneity differences between groups

Region	Cluster size	MNI coordinates	pAlphaSim correction
HAG<HCG: Orbital middle frontal gyrus			<0.01
HAG>HCG: Postcentral gyrus			<0.01

Under pAlphaSim<0.01, the abstinent group showed significantly lower ALFF values in the right orbital inferior frontal gyrus and left hippocampus (see Table 7 , Figure 6 [Figure 6: see original paper] and Figure 7 [Figure 7: see original paper]).

Correlation between abnormal ALFF values and total dose showed no significant correlations for right orbital inferior frontal gyrus (r=0.13, p=0.45) or left hippocampus (r=-0.10, p=0.58).

Table 7 Two-sample t-test for ALFF differences between abstinent and control groups

Region	Cluster size	MNI coordinates	pAlphaSim correction
HAG<HCG: Orbital inferior frontal gyrus			<0.01
HAG<HCG: Hippocampus			<0.01

3.5 Functional Connectivity Differences Between Heroin Abstinent and Healthy Control Groups

Compared to controls, functional connectivity was significantly enhanced between the right orbital inferior frontal gyrus and right caudate nucleus, and significantly reduced between the right orbital inferior frontal gyrus and right middle temporal gyrus as well as left precentral gyrus (see Table 8 , Figure 8 [Figure 8: see original paper], Figure 9 [Figure 9: see original paper], Figure 10 [Figure 10: see original paper]).

Correlation analysis between functional connectivity results and use duration (months) showed a significant negative correlation between use duration and functional connectivity between right orbital inferior frontal gyrus and right middle temporal gyrus (r=-0.37, p=0.03, see Figure 11 [Figure 11: see original paper]).

Table 8 Two-sample t-test for functional connectivity differences using right orbital inferior frontal gyrus as seed

Region	Cluster size	MNI coordinates	pAlphaSim correction
HAG>HCG: Right caudate			<0.01
HAG<HCG: Right middle temporal gyrus			<0.01
HAG<HCG: Left precentral gyrus			<0.01

This study examined the neural basis of heroin abstainers using functional connectivity, VBM, ReHo, and ALFF methods. ReHo and ALFF complement conventional functional connectivity analysis by revealing abnormal spontaneous neuronal activity and better localizing differential regions. Results showed that heroin abstainers with an average abstinence of 43.55 months exhibited significant differences in brain structure and function compared to healthy controls, suggesting that neural structural and functional features related to addiction persist nearly 4 years after withdrawal. This finding further confirms heroin' s impact on the brain.

Additionally, we found differences in brain structure and function related to different components of impulsivity in abstainers compared to normal controls after long-term use (including withdrawal). These findings provide evidence

for further understanding addictive impulsivity and offer more specific guidance and new perspectives for real-world relapse prevention.

Compared to controls, addicts showed reduced functional connectivity between the right orbital inferior frontal gyrus and left precentral gyrus. The precentral gyrus is associated with sensorimotor function; reduced connectivity between precentral gyrus and inferior frontal gyrus indicates reduced inhibitory control function in the dorsolateral prefrontal cortex where the inferior frontal gyrus resides, making it difficult to effectively control S-R habitual drug use behavior tendencies formed during long-term drug use and leading to impulsive drug use under drug-related cues.

One important characteristic of addicts is inability to control their drug use behavior. Two factors cause control system dysfunction: First, most addicts have impulsive personality traits related to familial genetic neural structural features (Ersche et al., 2013) that do not recover from drug use or abstinence and remain low-level, manifesting as low-level inhibitory control. Our finding of reduced connectivity between inferior frontal gyrus and left precentral gyrus may reflect the neural basis of this impulsive personality trait as inhibitory function.

Research shows that increased habitual behavior (reduced "goal-directed" control) correlates partially with motor impulsivity personality traits measured by impulsivity scales; habitual (difficult-to-inhibit automated) behavior is an important manifestation of such personality (Hogarth et al., 2012). From this perspective, stopping impulsivity/response inhibition function may be a characteristic feature of impulsive personality traits. Addicts and their siblings show significantly increased gray matter volume in the putamen compared to controls (Morein-Zamir & Robbins, 2015), indicating that motor impulsivity (response inhibition) corresponding to habitual behavior exists before addictive behavior as a personality trait and serves as a susceptibility factor for addiction (promoting transition of drug use to habitual behavior) because it cannot control drug use behavior that has already occurred.

Second, long-term heroin use may cause further irreversible damage to inhibitory control function (Fu et al., 2008). Our study found that nearly 4 years after withdrawal, with weakened drug effects, addicts' low inhibitory neural basis persists. This low inhibitory characteristic coexists with impulsive personality traits before drug use and shares neural basis, further illustrating a typical feature of impulsive personality traits: low inhibitory control. Of course, low inhibitory characteristics could also result from long-term drug use, which we cannot determine. However, as previously mentioned, trait impulsivity existing before cocaine use correlates with structural abnormalities in the prefrontal-(ventral)striatal pathway (Ersche et al., 2013), with reduced white matter density in right inferior frontal gyrus and increased gray matter volume in putamen. Moreover, addicts' siblings who have never used addictive substances show similar brain activation and gray matter volume changes (Ersche et al., 2012; Morein-Zamir & Robbins, 2015). Therefore, some imaging manifestations in heroin abstainers may predate

heroin use, expressed as personality traits. Such traits, based on abnormal neural mechanisms, make it more difficult for them to control drug use behaviors driven by various drive forces after drug use, leading to addiction.

Additionally, compared to controls, HAG showed significantly enhanced functional connectivity between orbital inferior frontal gyrus and right caudate nucleus, and significantly reduced ALFF values in right orbital middle frontal gyrus and left hippocampus. Enhanced connectivity between orbital inferior frontal gyrus and right caudate nucleus is a neural mechanism of compulsive behavior (Grusser et al., 2004). When addicts already have low inhibitory control, uncontrollable compulsive drug use is more likely to occur. Although theoretically, later-stage addictive behavior is primarily habitual drug use under relevant cues, with neural mechanisms depending more on connectivity between dorsolateral striatum (putamen) and prefrontal inhibitory control-related brain regions (Zeng et al., 2018), if this automated habitual behavior tendency is not realized (e.g., cue reactions in laboratory settings or drug unavailability in reality), this automated action tendency transforms into intense craving and drug-seeking motivation, which may evolve into compulsive drug use behavior in real life.

The orbital frontal region is related to the motivation system; its neuronal activity disturbance indicates impaired motivational function in addicts. Nucleus accumbens/ventral striatum, subgenual/rostral anterior cingulate, anterior prefrontal cortex, and orbital frontal cortex are main components of the reward system (Zilverstand et al., 2018). ReHo and functional connectivity results indicate that nearly 4 years after withdrawal, heroin addicts still have neural basis for drug use driven by reward effects, which may still be triggered under certain conditions.

Significantly increased ReHo values in the postcentral gyrus indicate increased consistency of neuronal activity (in time series) in this region with good synchronization, representing abnormal activation of somatosensory cortex related to cognition and emotional sensation. This is usually associated with heroin-related cue reactions (Wei et al., 2019). This study did not present drug-related cues; increased ReHo in postcentral gyrus indicates that addicts still retain automated drug use behavior tendency reactions despite approximately 4 years of abstinence. The postcentral gyrus is not a typical region for inhibitory response activation but is often associated with responses under no-go cues; its activation leads to responses when they should be stopped, increasing relapse risk (Prisciandaro et al., 2013). This overactivation of sensorimotor brain regions manifests as habitual drug use behavior tendency under relevant cues in addictive behavior (Zeng et al., 2018), representing strong motor impulsivity—an important regulatory factor for impulsive behavior that cannot control drug use impulses caused by relevant cues. This factor persists after withdrawal, showing that the neural basis constituting impulsive inhibitory control in addicts remains nearly 4 years after withdrawal.

However, Wang et al. (2016) found that strictly abstinent heroin addicts (>3 years) showed significantly reduced functional connectivity between bilateral

postcentral gyrus and cuneus compared to healthy controls, indicating impaired postcentral gyrus function. Gardini and Venneri (2012) found reduced gray matter volume in postcentral gyrus in methadone-maintained heroin abstainers, indicating structural abnormalities. He et al. (2008) found gray matter recovery in postcentral gyrus in heroin-dependent individuals 2 months after drug cessation. Thus, postcentral gyrus structural and functional recovery appears related to different withdrawal treatment methods; complete abstinence may be more beneficial for postcentral gyrus recovery than methadone maintenance, though this inference requires more research verification.

Significantly reduced functional connectivity between orbital inferior frontal gyrus and right middle temporal gyrus and left precentral gyrus leads to reduced inhibitory function for behavioral actions generated by motor brain regions, indirectly indicating that S-R behavioral responses formed through associative learning—that is, habitual drug use behaviors directly triggered by relevant cues —are characteristic of this stage (Hu et al., 2015). This also shows that relevant cue reactions are important driving forces for addictive behavior, consistent with drug use characteristics of addicts in real-life addiction processes.

Additionally, the precentral gyrus belongs to the ventral attention network (Zhang et al., 2017)/ventral frontoparietal attention network, namely the salience network, which is the main neural basis for relevant cue reactions, promoting attentional bias toward drug-related cues and inducing impulsive drug use behavior.

These results are consistent with the iRISA model hypothesis. Reward/motivation networks related to orbital frontal cortex, memory networks related to hippocampus, and habit networks related to caudate nucleus all participate in addiction processes (Zilverstand et al., 2018). Functions of these brain regions can not only strengthen addictive substance effects but also form drug action memories through associative learning, responding in a conditioned reflex manner when relevant cues appear, making addicts exhibit difficult-to-inhibit habitual drug use behavior and showing strong motor impulsivity. From this perspective, abnormal functional connectivity in reward, memory, and habitual behavior brain regions may be the neural basis driving addict impulsivity and can be understood as the driving force of addictive impulsivity, promoting habitual and compulsive drug-seeking and use behavior.

These brain regions show abnormal activation and functional connectivity patterns in addicts, and their structures gradually become abnormal. This study observed abnormal functional connectivity and structural changes in the above drive-related brain regions in addicts after nearly 4 years of abstinence, proving that drive functions related to addictive impulsivity remain abnormal regardless of current drug use. This is consistent with relevant research (Zilverstand et al., 2018).

Compared to controls, HAG showed significant differences in total gray matter volume and brain volume, with significantly reduced gray matter volume in the

right medial superior frontal gyrus. This indicates that long-term heroin use causes brain gray matter atrophy and substantial brain damage that does not recover with abstinence. This is consistent with findings that long-term heroin addicts (7 days abstinent) have lower cortical thickness in superior frontal regions compared to healthy controls (Li et al., 2014). The superior frontal gyrus is related to working memory (du Boisgueheneuc et al., 2006) and subjective reported drug use intention and tendency (Hassani-Abharian et al., 2015). Fu (2008) suggested that the superior frontal gyrus is overactivated during response inhibition tasks to compensate for executive functions of ventral prefrontal cortex and anterior cingulate cortex. Reduced gray matter volume in superior frontal gyrus may lead to working memory impairment, reduced short-term storage capacity, and information management difficulties, thereby affecting response inhibition function.

Gray matter volume in the right middle temporal gyrus and left medial paracingulate gyrus of HAG decreased with increasing drug dose. This result supports Yuan' s (2009) finding that gray matter density in temporal lobe and cingulate cortex is lower than healthy controls and negatively correlates with heroin use duration, suggesting a cumulative effect of heroin use.

Consistent with Liu (2009) and Wollman (2015), cingulate cortex gray matter volume showed atrophy, with left cingulate damage increasing with heroin use duration. The paracingulate gyrus is part of ventral prefrontal cortex (Gallagher et al., 2000) and is often observed to be activated independently of task type in various cognitive processes (Zhang et al., 2017). The medial paracingulate gyrus belongs to the self-directed/reference network activated during self-directed cognitive processes, supporting higher cognitive regulatory functions (such as self-awareness and self-reflection) and correlating with self-reported craving and use impulses. Abnormal activity in this network may reduce ability to participate in non-self-directed cognitive demand tasks, meaning addicts have difficulty guiding themselves toward correct decisions when having drug use goals. This also indicates that even after long-term abstinence, deficits in higher cognitive functions such as self-awareness and self-regulation still prevent addicts from regulating their drug use behavior, manifesting as high relapse risk under relevant cues.

In summary, addicts show abnormalities in both structure and function of neural bases related to inhibitory control, reward-based decision-making, and habitual behavior, indicating low control system function. This control system does not change with long-term abstinence, proving its association with impulsive personality traits existing before addiction. Meanwhile, neural bases of reward and S-R effects also show abnormal status; both forces are drives for drug use. When weak inhibition and strong drive neural bases coexist, the possibility of relapse behaviors such as habitual drug use under relevant cues or compulsive drug use due to craving increases, even after long-term abstinence. This further illustrates that neural mechanisms causing addictive impulsivity are multifaceted, including both low inhibitory control problems existing before

substance use and drive effects formed through reward effects and relevant cue reactions during long-term drug use, as well as changes from withdrawal itself.

Our results differ from Wang et al. (2012), who found that abnormal gray matter in superior frontal gyrus could return to normal 1 month after withdrawal in heroin-dependent individuals. In our study, gray matter volume in superior frontal gyrus did not recover after an average of 43.55 months. One possible reason is that some heroin abstainers in our study simultaneously received methadone maintenance treatment, while Wang' s subjects abstained from all opioid drugs. As an extended opioid dependence drug, methadone has similar effects to addictive drugs to some extent, and heroin users receiving methadone treatment are considered to remain in an addicted state (Connock et al., 2007). Studies have found that methadone-maintained patients show worse performance than completely abstinent individuals in attention tests (Tabatabaei-Jafari et al., 2014) and exhibit higher cue-induced activation in mesolimbic regions, visual-spatial attention regions, memory retrieval regions, and somatosensory cortex (Wei et al., 2019). In abstinence-based treatments, avoidance of addictive drugs may be achieved through prefrontal regulation of emotion and decision-making, while in methadone maintenance treatment, heroin abstinence is achieved through methadone' s chemical effects on opioid receptors in reward circuits (Tabatabaei-Jafari et al., 2014). Therefore, our results may not be entirely attributable to heroin abstinence due to partial methadone use. Although our analysis showed no significant differences in brain metrics between the two groups, we cannot exclude functional differences across brain regions. The impact of methadone on addicts' neural mechanisms needs to be deeply clarified to provide further data support for future substitution therapies. Future research could compare heroin abstainers in substitution therapy versus complete abstinence using different neurofunctional analyses, such as task-state PPI analysis.

Additionally, this study primarily used voxel-based morphometry to observe brain gray matter density changes after drug cessation. Even positive changes cannot confirm recovery due to withdrawal because we cannot determine subjects' pre-drug use neural baseline. Given the operational unlikelihood of such research, future studies could compare psychological and imaging manifestations of abstainers with their immediate family members with similar personality traits, potentially clarifying drug use and withdrawal effects on brain function and structure while controlling for pre-existing neural abnormalities. Finally, stress and negative emotional states are important relapse factors and indirect drives that can serve as relevant cues triggering habitual drug use in real life. Corresponding brain regions are primarily emotion-related; how connectivity between these regions and automated behavior neural basis brain regions and inhibitory control brain regions changes under drug or withdrawal effects is complex and requires specialized research. Due to length limitations, this paper mainly discusses mechanisms of inhibitory control, reward effects, and habitual behavior.

After nearly four years of abstinence, addicts still show abnormal status in reward, salience, and habitual behavior network systems, with significant differences from healthy controls. This may be because drive factors causing drug use have not weakened, while inhibitory control as a personality trait remains low-level and cannot regulate strong drive effects caused by relevant cue reactions, presenting high impulsivity and relapse risk. Additionally, no significant correlations were found between impulsivity-related brain regions and abstinence duration, indicating that neurophysiological differences between addicts and normal individuals do not recover with increased abstinence time. This suggests that heroin addicts may have innate neurostructural differences and that heroin-induced damage may be long-term or even permanent. Moreover, as total drug dose during addiction increases, gray matter volume in right middle temporal gyrus and left medial paracingulate gyrus shows significant decreasing trends, indicating that heroin has cumulative effects that directly damage addicts' inhibitory control neural function and structure.

Future relapse prevention interventions should focus on both impulsivity drive sources and control capacity. Additionally, methadone substitution treatment effects on brain function recovery need consideration to find psychorehabilitation methods compatible with complete abstinence.

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