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Dysfunctional connectivity patterns in chronic heroin users: An fMRI study

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ABSTRACT

Recent functional neuroimaging studies have examined cognitive inhibitory control, decision-making and stress regulation in heroin addiction using a cue-reactivity paradigm. Few studies have considered impairments in heroin users from an integrated perspective for evaluation of their brain functions. We hypothesized that the brain regions that are dysregulated in the chronic heroin users during cue-reactivity studies may also show dysfunctional connectivity in memory, inhibition and motivation-related dysfunctions during a resting state free of cues. The present study used resting functional magnetic resonance imaging (fMRI) to compare the interaction of brain regions between 12 chronic heroin users and 12 controls by employing a novel graph theory analysis (GTA) method. As a data-driven approach, GTA has the advantage of evaluating the strength as well as the temporal and spatial patterns of interactions among the brain regions. Abnormal topological properties were explored in the brain of chronic heroin users, such as the dysfunctional connectivity in the prefrontal cortex, ACC, SMA, ventral striatum, insula, amygdala and hippocampus. Our results suggest that GTA is a useful tool in defining dysregulated neural networks even during rest. This dysfunctional brain connectivity may contribute to decrease self-control, impaired inhibitory function as well deficits in stress regulation in chronic heroin users.

With the development of medical equipment and modern imaging processing technologies, many scientific breakthroughs have occurred regarding the mechanisms underlying drug addiction. Similar to other drug-related studies [9], heroin addiction is complex disease of the brain, involving both affective and cognitive processes [5]. Several brain regions in either heroin or cocaine addiction have been reported to show functional unconventionality in some cue-reactivity paradigms, including the insula, anterior cingulate cortex (ACC), amygdala, orbitofrontal cortex (OFC), cingulated cortex, and temporal cortex [11,27].

Numerous laboratories have shown that individuals who are addicted to heroin demonstrate a phenomenon known as cue-reactivity in which drug-related cues cause significant psychophysiological reactions. In the past few years, many cue-reactivity studies with heroin addicts have strongly supported the assertion that addicts have significant cue-specific reactions to drug-related stimuli. Furthermore, studies have shown an association between drug-related cue activation and several brain circuits that previous research has shown to be implicated in decision-making, inhibitory control, stress regulation and assigning emotional valence [10,11,20].

Recent studies have begun to view drug addiction from an integrative perspective (e.g. functional interplay among different drug-affected circuits). The functional integration of different brain regions in perception and behavior is a functional principle of brain organization in higher vertebrates [8,22]. Li and Sinha [12] integrated previous results [2–4] to hypothesize that in patients with psychostimulant dependence, dysfunction in the prefrontal cortex (PFC)–ACC circuit renders them susceptible to compulsive drug seeking especially during conditions of high stress and arousal, and it is marked by increased activity in the limbic-striatal circuits comprising the amygdala, hippocampus, and dorsal striatum. Thus, Li and Sinha suggested that increased processing in the PFC–ACC results in adequate inhibitory control and low craving levels, and in states with hypoactivity of the PFC–ACC circuits, activity of the stress and reward centers is increased, and this increased compulsive drug-seeking behavior leads to a higher susceptibility to

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Table 1
Demographic characteristic of subjects.

Information	Non-drug users	Chronic heroin users
Age (years)	35.4 ± 7.1	41 ± 5.6
Education (years)	9.1 ± 2.8	8.2 ± 1.8
Duration of heroin use (years)	N/A	16.0 ± 3.5
Dosage of heroin use (g/day)	N/A	1.0 ± 0.7
Duration of abstinence from heroin (months)	N/A	6.0 ± 10.6

drug use and relapse. Therefore, future studies from an integrative systems perspective may play a key role in understanding the mechanisms underlying compulsive drug use behaviors. However, few studies have focused on this issue.

The exact mechanisms underlying heroin addiction are not fully understood, and we hypothesized that the brain regions that are dysregulated in the chronic heroin users in cue-related studies may also show dysfunctional connectivity in memory, inhibition and motivation-related dysfunctions during a resting state free of cues. To characterize the dysfunctional pathways caused by heroin addiction, the method of graph theory analysis was used. According to previous studies, numerous networks and cognitive functions, such as memory, planning, and abstract reasoning, in the brain are constantly changing and interacting with other proximal or distal regions [16,24]. Graph theory analysis has the advantages of evaluating the strength as well as the temporal and spatial patterns of interactions in the brain [16]. This approach has been applied in many previous brain network studies, with convincing results [1,17].

The experimental protocol was approved by Institutional Review Board of The Fourth Military University, China. Twelve abstinent male heroin-dependent patients (HDP, right-handed, age 41 ± 5.6 years, range 34–54 years) were enrolled from a local inpatient treatment research facility, and 12 healthy right-handed individuals (HI, male, age 35.4 ± 7.1 years, range 26–51 years) were recruited from the local community. All potential volunteers had a minimum of a nine-grade education and two groups were matched in terms of education and geographic location, and were fully informed of the nature of the research and had given written consent. All HDP volunteers met DSM-IV criteria for heroin dependence. They regularly used cigarettes and denied any psychotropic agent in the 3 months before the fMRI scan. All HDP had a mean heroin dependence history of 16.0 ± 3.5 years (range 10–20 years), a prior mean dosage per day of 1.0 ± 0.7 g (range 0.2–3.0 g), mean abstinence from heroin of 6.0 ± 10.6 months (range 1–25 months), negative test for the presence of morphine in urine-analysis (reagent box produced by China Carrie City International Engineering Co.) and presence of human HIV in blood test. None of the HDP had a history of neurological illness or injury with the exception of drug addiction. All HI only allowed occasional social use of alcohol and cigarettes, and they reported no used of psychoactive substances during the 72 h before the fMRI scan. No HDP displayed overt behavioral signs of heroin intoxication. None of the subjects were taking prescription drugs within 1 week that affected the central nervous system, had a history of neurological illness. None of the subjects were previously exposed to a high magnetic field (Table 1).

This experiment was carried out in a 3T GE scanner. A gradient echo T2*-weighted sequence with in-plane resolution of 3.75 mm × 3.75 mm (TE 30 ms, TR 2 s, matrix 64 × 64, field of view 240 mm, and flip angle 90°) and a set of T1-weighted high-resolution structural images (TE 3.39 ms, TR 2.7 s, matrix 256 × 256, field of view 256 mm, flip angle 7°, in-plane resolution 1 mm × 1 mm, and slice thickness 1 mm) were acquired.

For the resting scanning, data were preprocessed by removing the first five time-points to eliminate nonequilibrium effects of magnetization. The remaining time-points (150 volumes) were used for functional connectivity analysis. All functional images were processed using the following steps: (i) compensation of systematic, slice-dependent time shifts, (ii) elimination of systematic odd–even slice intensity differences due to interleaved acquisition, (iii) rigid body correction for geometrical displacements caused by head movement, and (iv) coregistration with the Montreal Neurological Institute (MNI) echoplanar imaging (EPI) template image. The preprocessing steps used SPM5 software. The data were not spatially smoothed.

We applied several processing steps to optimally condition the functional data for the analysis of voxel-bases correlations. The normalized data were filtered using a bandpass filter (0.01–0.1 Hz) to reduce the effects of low-frequency drift and high-frequency noise. To reduce the effects of spurious variation, several sources were removed from the data via linear regression: six parameters obtained by rigid body correction of head motion, the signal averaged over the whole brain, the signal averaged over the lateral ventricles, and the signal averaged over a region centered in white matter. This regression procedure can be used to remove fluctuations unlikely to be involved in specific regional correlations. Removal of the global signal would cause a shift in the distribution of correlation coefficients and make interpretation of the sign of the correlation ambiguous [13]. For this reason, we chose a relatively strict threshold for our network analysis.

We used the anatomically labeled template image used previously by Tzourio-Mazoyer [23], and the registered fMRI data divided the whole brain into 90 ROIs (45 for each cerebral hemisphere, Table 2). The manner in which the brain was divided has been used in several previous studies [1,17]. We extracted the regional mean time series by averaging the fMRI time series of all of the voxels in each of the 90 ROIs over the entire brain.

Partial correlation was used to construct undirected graphs [17]. We first had to relate the threshold ($\bar{r}_{thre}$) with the partial correlation coefficient (r_{ij}) so that each statistically significant connection could be represented as an undirected edge if r_{ij} exceeds $\bar{r}_{thre}$. Thus, edges between regional nodes presented the whole-brain functional network. This method has the advantage of simultaneously visualizing the connectivity patterns of all 90 ROIs. We then defined a graph as having 90 nodes (in this study, ROIs) and edges (functional connections). The key parameters of the network are the clustering coefficient C and the mean minimum path length L. The clustering coefficient $0 < C_i < 1$ is a ratio that defines the proportion of possible connections that actually exist between the nearest neighbors of a ROI [26]:

$$C_p = \frac{1}{90}\sum_{j=1}^{90}\frac{\#E_j}{\#V_j(\#V_j - 1)/2}$$

where $\#E_j$ is the number of edges connecting neighbors of ROI j, and $\#V_j$ is the number of neighbors of ROI j. The minimum path length L_p is the average of the shortest path length over each possible pair of vertices:

$$L_p = \frac{1}{4005}\sum_{s=1}^{89}\sum_{k=s+1}^{90}\min\{L_{i,j}\}$$

where $\{L_{i,j}\}$ is the shortest path length between the ith node and the jth node, and the path length is defined as the number of edges included in the path.

Small-world are attractive models for connectivity of nervous systems because the combination of high clustering and short path length confers a capability for both specialized or modular processing in local neighborhoods and distributed or integrated processing over the entire network [1]. We examined the ratio $\gamma = C_{net}/C_{rand} > 1$

Table 2
Cortical and subcortical regions defined by the AAL template image in standard stereotaxic space.

Region	Abbreviation	Region	Abbreviation
Superior frontal gyrus, dorsolateral	SFGdor	Superior temporal gyrus	STG
Superior frontal gyrus, orbital	ORBsup	Superior temporal gyrus, temporal pole	TOPsup
Superior frontal gyrus, medial	SFGmed	Middle temporal gyrus	MTG
Superior frontal gyrus, medial orbital	ORBsupmed	Middle temporal gyrus, temporal pole	TOPmid
Middle frontal gyrus	MFG	Inferior temporal gyrus	ITG
Middle frontal gyrus, orbital	ORBmid	Heschl gyrus	HES
Inferior frontal gyrus, opercular	IFGoperc	Hippocampus	HIP
Inferior frontal gyrus, triangular	IFGtriang	Parahippocampal gyrus	PHG
Inferior frontal gyrus, orbital	ORBinf	Amygdala	AMYG
Gyrus rectus	REC		
Anterior cingulate gyrus	ACC	Insula	ANG
Olfactory cortex	OLF	Thalamus	THA
		Caudate nucleus	CAU
Superior parietal gyrus	SPL	Lenticular nucleus, putamen	PUT
Paracentral lobule	PCL	Lenticular nucleus, pallidum	PAL
Postcentral gyrus	PoCG		
Inferior parietal gyrus	IPL	Calcarine fissure and surrounding cortex	CAL
Supramarginal gyrus	SMG	Cuneus	CUN
Angular gyrus	ANG	Lingual gyrus	LING
Precuneus	PCUN	Superior occipital gyrus	SOG
Posterior cingulate gyrus	PCC	Middle occipital gyrus	MOG
		Inferior occipital gyrus	IOG
Precentral gyrus	PreCG	Fusiform gyrus	FFG
Supplementary motor area	SMA		
Rolandic operculum	ROL		
Median- and para-cingulate gyrus	DCG		

and the ratio $\lambda = L_{net}/L_{rand} \approx 1$ in small-world networks [26]. The ratio $\delta = \gamma/\lambda$ can be summarized for small-world networks as typically being >1 [1].

After we calculated the 90×90 partial correlation matrix from each individual within the non-drug user group, the mean functional connectivity matrix was computed by averaging the entire partial correlation matrix. To obtain better normality of partial correlation coefficients, we used Fisher's *r*-to-*z* transformation and related the threshold $\bar{r}_{thre}$ to the functional connectivity matrix. We then created an unweighted binary graph so that the nodes were connected if the partial correlation coefficients exceeded the threshold. Furthermore, the results of a co-variate analysis of age were almost the same as the results in this study. The mean path length of the network was $L_{HI} = 4.8$, with a clustering coefficient of $C_{HI} = 0.17$. Compared with random graphs corresponding to the number of nodes, mean degree, and degree distribution, the network of non-drug users had an almost identical path length ($\lambda_{HI} = 1.548$) but was more locally clustered ($\gamma_{HI} = 7.727$), resulting in a small-world scalar of $\sigma_{HI} = \gamma_{HI}/\lambda_{HI} = 4.99$. Results of the topological properties of non-drug users showed that intra-hemispheric local regions shared vital connections with nearby anatomical areas. The pattern of this network was consistent with many previous studies of functional connectivity during the resting state [1,17] (Fig. 1A).

Using the same procedures and threshold as in the analysis of the non-drug users' network, we created a functional network for chronic heroin users. The mean path length of the network was $L_{HDP} = 4.1$, with a clustering coefficient of $C_{HDP} = 0.19$. Its ratio of λ_{HDP} was 1.548 and γ_{HDP} was 7.727, resulting in a small-world scalar of $\sigma_{HDP} = \gamma_{HDP}/\lambda_{HDP} = 2.12$. From the network results of the two groups during the resting state, we found apparent small-world properties of both groups. λ was approximately equal to 1 and γ was significantly greater than the value of 1 at the threshold of $\bar{r}_{thre}$ whereas chronic heroin users' small-world scalar is $\sigma_{HDP} = 2.12$, which was much smaller than that of non-drug users ($\sigma_{HI} = 4.99$). The significant small-world scalar difference between the two group means consisted of distorted small world properties in chronic heroin users. Thus, from their topological map, we can see that the topological properties significantly changed in many brain regions (Fig. 1B).

Because the two groups' networks were created under the same threshold and their small-world scalars were significantly different, we estimated the degree of connectivity difference between these two groups. In graph theory, the degree of a vertex of a graph is the number of edges incident to the vertex, and it was defined as the number of voxels across the brain that showed strong correlation with the target voxel. For each predefined ROI, the degree of connectivity was calculated in both chronic heroin users' and non-drug users' networks. Despite having the same threshold, the difference in degree of each ROI difference between the two groups could be used to detect the dysfunctional brain region. Results showed that connectivity strength was higher overall in the ACC, supramarginal motor area (SMA), hippocampus, amygdala, insula, putamen, pallidum, caudate, dorsolateral part of the superior frontal gyrus (SFGdor), and orbital part of the inferior frontal gyrus in chronic heroin users compared with non-drug users (Fig. 2).

In this investigation, we viewed heroin addiction problems from a functional integration perspective. Graph theory was used to build the network for both chronic heroin users and non-drug users, which allowed us to compare the topological properties of functional brain networks between these two groups. Evidence from the non-drug users' network showed significant small-world properties, consistent with several previous studies [1,17]. However, the chronic heroin users' network showed a lower small-world scalar under the same threshold, demonstrating more variable topological properties (Fig. 1B). After the statistical analysis, dysfunctional connectivity was found among several brain regions in the chronic heroin users' network. Interestingly, these regions could be further divided into several categories, and each category could be associated with specific neural circuits that are affected by drug addiction and associated with decision-making, inhibitory control, stress regulation, and working memory. Despite several different pathological traits, common dysfunctions may be shared between heroin and cocaine addiction. This inference needs further investigation in future research [11].

When comparing absolute brain regions, the degree of the SFGdor and ORBinf was significantly higher in chronic heroin users' networks than that of non-drug users (Fig. 2). The location of the

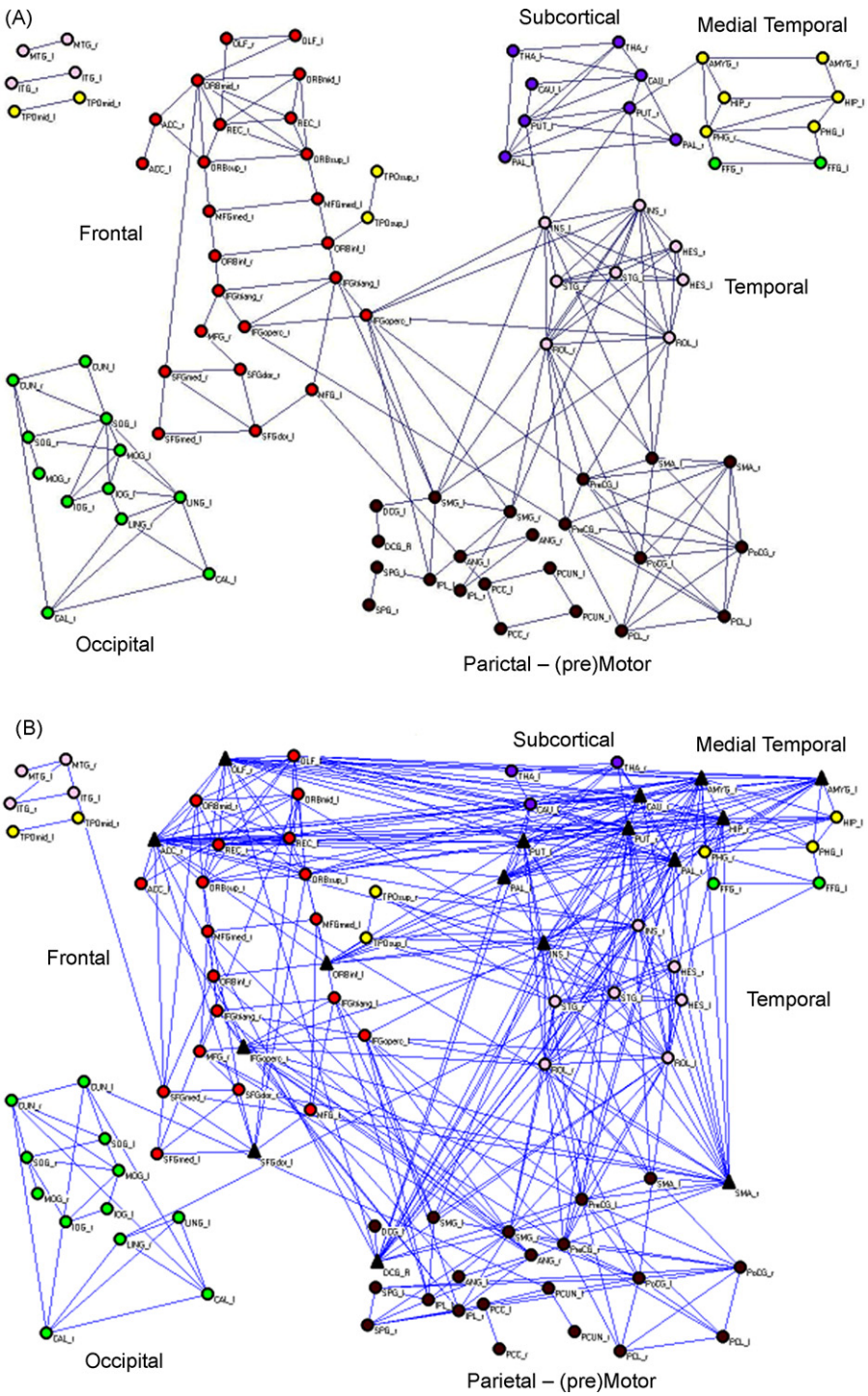

Fig. 1. Topological map of non-drug users' (A) and the chronic heroin users' (B) brain functional networks during the resting state. Network of regions in six main groups designated as the medial temporal (yellow), subcortical (purple), temporal (pink), parietal-(pre)motor (brown), frontal (red) and occipital (green). Black triangles represent the most remarkable connectivity strength changes with the chronic heroin users being higher than in non-drug users (two-sample t-test $p < 0.05$). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

ORBinf is in the orbital part of the frontal cortex, and its main portion is located in the OFC. The SFGdor is part of the dorsolateral PFC. Thus dysregulation of these brain regions may reveal dysfunctional connectivity in the OFC and dorsolateral PFC in chronic heroin users. The PFC is largely considered to be involved in the management of integrating motivational and cognitive information and in mediating the neural basis for adaptive processing of incentive stimuli [27], but it may fail to adequately monitor and stimulate stress during human drug craving [9]. As mentioned above, the abnormal functional connectivity of the PFC in chronic heroin users may lead to poor monitoring function in daily life. Thus, we inferred that the disruption of monitoring function in these areas during the resting state may result in abnormal performance in a cue-reactivity test in drug-addicted individuals.

Compared with the non-drug users' network, the ACC and SMA also showed irregular connectivities in the heroin-addicted group (Fig. 2). Heroin-addicted patients have traits of uninhibited behavior and loss of self-control, and the motivation to obtain drugs

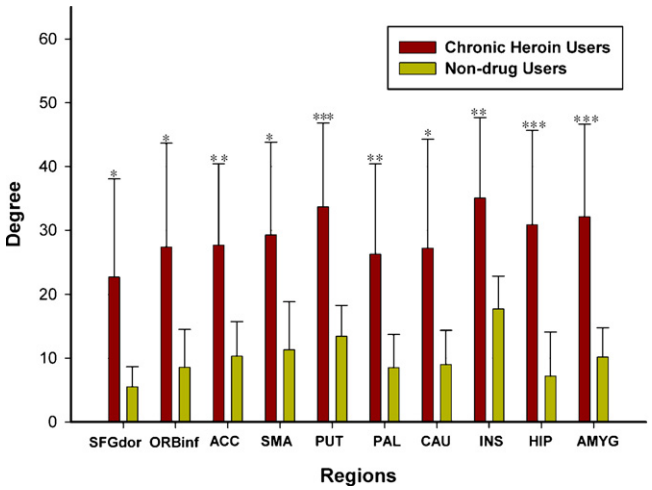

Fig. 2. Comparison of the degrees of differences between chronic heroin users and non-drug users. Presented here are the most significant ROIs after a two-sample *t*-test. The black bars are the results from the chronic heroin users' network, and the gray bars are the results from that of non-drug users. Error bars are based on a 95% confidence interval. $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$ (Fisher's exact test).

overpowers the drive to achieve other non-drug-related goals [9]. Furthermore, several previous studies have reported that inhibitory control behavior is monitored by the ACC and SMA [6,10,11]. According to our findings, the irregularity of the ACC and SMA may cause inhibitory control to become weaker in heroin-addicted patients. Our results support the hypothesis that chronic heroin abuse leads to destructive changes in brain regions that cause poor inhibitory control; thus, having uninhibited behavior and loss of self-control in processing drug-related cues becomes easier. This may also help to explain why inhibitory control always showed unusual activation during a GO-NOGO task in chronic heroin users.

The present results also showed that the caudate, putamen, and pallidum had dysregulated functional connectivity in the heroin-addicted network compared with non-drug users. Anatomically, these regions are major parts of the striatum. Shaham [18] showed that exposure to intermittent footshock stress reliably reinstated heroin seeking in rats after prolonged drug-free periods. From positron emission tomography studies, acute stress exposure was shown to increase dopamine release in the ventral striatum [15], and these studies also showed that the ventral striatum is associated with stressful experiences and reward processing. Dysregulation of the striatum was also shown in our study, and this may lead to unusual stress-related brain activation during the resting state in heroin-addicted individuals. Our inferences are consistent with previous studies [21]. Shalev [19] depicted neuronal mechanisms underlying stress-induced reinstatement of heroin-seeking behavior. We hypothesized that a deficit in stress regulatory processes may occur in heroin-addicted patients during the resting state. When patients were influenced by drug-related cues, their emotional stress heightened, possibly leading to poor decision-making and drug use [12].

Interestingly, we also found a significantly degree of the insula in chronic heroin addicts network (Fig. 2). The insula has multiple functions, such as integrating information, collecting somatic sensory information, and regulating emotions and feelings from multiple cortical areas. Furthermore, the insula can receive information from "homeostatic afferent" sensory pathways via the thalamus and sends outputs to other limbic-related structures, such as the amygdala, striatum, and OFC [7]. Several studies have recently found that smokers with brain damage in the insula were more likely to quit smoking easily and without relapse, suggesting that the insula plays a role in the sensation that smoking itself is a conscious psychosomatic necessity [7,14]. Nicotine and heroin share the same mechanism in stimulating dopamine release. Therefore, we suggest that insula-related activity is abnormal in heroin-addicted patients during the resting state compared with the non-drug users, possibly leading to addictive behaviors.

The amygdala and hippocampus are involved in the mesolimbic dopamine circuit, which is associated with drug reinforcement as well as memory and craving responses [9]. Based on our present observations, the amygdala and hippocampus were significant in degree comparisons (Fig. 2). Dysfunction of these regions in chronic heroin users during the resting state was accompanied by working memory-related activities.

Decreased monitoring, failure of inhibitory control, and dysfunctional stress responses are likely to occur in chronic heroin users. Normally, these circuits operate simultaneously and interact with each other, and the brain employs these mechanisms to optimize coping responses in daily life. However, these circuits were found to be significantly different between chronic heroin users and non-drug users, possibly attributable to the fact that reciprocity of these circuits was deficient and the integrative systems of functional connectivity during the resting state were dysregulated in heroin-addicted patients, thus leading to maladaptive behaviors. As shown in Fig. 1, the network of drug-addicted patients was more disorganized compared with matched controls. Significant dendritic branching and spine density results from repeated drug administration [25], possibly causing the irregular pathways in the chronic heroin users' network and leading to irregular brain circuitry.

Our results show that dysfunctional integrations occur in the brains of heroin-addicted individuals during the resting state (Figs. 1 and 2). We suggest that this dysregulation of brain regions may lead to a decrease in the brain's monitoring function, impairing inhibitory control and inducing deficits in stress regulation. These findings may help us better understand the mechanisms underlying heroin addiction. Further studies are warranted to detect the reciprocal roles of each circuit that is affected by drug addiction.

As a result, our analyses of dysfunctional brain network for heroin-dependent patients limited to a set of 90 predefined ROIs. Therefore, we may not have described fifil aspect characteristic of network. Further evidences are needed to investigate the brain functional network in more precise partition of the whole-brain region. On the other hand, for the limitations of data collection, age was significantly different between two groups, however, several researches found the stable structure of network of GTA in healthy adults during resting state. Different age between HDP and HI did not qualitatively change the results for GTA. Next study we would consider the age-, and gender-matched individuals.

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