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Altered small-world brain functional networks and duration of heroin use in male abstinent heroin-dependent individuals

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ABSTRACT

Although previous studies reported addiction-related alteration in resting-state brain connectivity, it is unclear whether these resting-state connectivity alterations were associated with chronic heroin use. In the current study, graph theory analysis (GTA) was applied to detect abnormal topological properties in heroin-dependent individuals. Several statistical parameters, such as degree (D), clustering coefficient (C) and shortest absolute path length (L), were included to test whether or not there was significant correlation between these parameters and the duration of heroin use. Our results demonstrated abnormal topological properties in several brain regions among our heroin-dependent subjects. Some of these regions are key areas of drug addiction-related circuits (control, reward, motivation/drive and memory), while others are involved in stress regulation. In addition, the duration of heroin use was positively correlated with the parameter D in the right parahippocampal gyrus, left putamen and bilateral cerebellum, but negatively correlated with the parameter L in the same regions. Our findings suggested that there is abnormal functional organization in heroin-dependent individuals and that the duration of heroin use is a critical factor leading to the altered brain connectivity.

Drug addiction, characterized by a compulsive drive to take drugs despite serious negative consequences, is a disorder that involves complex interactions between biological and environmental variables [12]. Over the past few decades, numerous imaging studies have revealed neurochemical and functional changes in the brains of drug-addicted subjects, which provide new insights into the mechanisms underlying addiction [4,12,18,25]. Volkow et al. proposed a model consisting of four circuits involved in drug abuse and addiction: (1) reward, located in the nucleus accumbens (NAc) and ventral pallidum; (2) motivation/drive, located in the orbitofrontal cortex (OFC) and subcallosal cortex; (3) memory and learning, located in the amygdala and hippocampus; and (4) control, located in the prefrontal cortex and anterior cingulate gyrus (ACC). In this model, drug addiction was considered as a state initiated by the qualitatively different and larger reward value of the drug, which triggers a series of adaptations and changes in reward, motivation/drive, memory, and control circuits of the brain. These functional changes result in an enhanced and permanent saliency value for the drug and loss of inhibitory control, finally leading to the emergence of compulsive drug administration and relapse [29]. In addition, many researchers revealed that emotional stress also contributes to drug addiction [26,28]. Exposure to stress has been shown to aggravate drug craving and related increases in drug craving and relapse [6,27]. These identifications designate the complexity of drug addiction. Unfortunately, most previous heroin studies mainly focused on deficits in the specific circuit employing task-related methods [8]. Fu et al. reported impaired response inhibition function in abstinent heroin dependents employing GO/NOGO association task [8]. To date, few studies systematically investigated heroin addiction during resting-state.

Recently, studies employing functional magnetic resonance imaging (fMRI) have delineated human brain's resting-state networks [2,7,14], suggesting correlated spontaneous activity occurs within spatially distinct, functionally related groups of brain regions during task-free conditions [14,22]. Blood-oxygen-level-dependent (BOLD) signal fluctuations within these resting-state networks occur at low frequencies (0.01–0.08 Hz) [7]. In addition, assessments of resting-state networks have been conducted in brain disorders investigating the level of integration of brain sys-

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tems when no tasks were performed [9,30], such as in Alzheimer's disease (AD) [30] and schizophrenia [9]. The decreased connectivity between the hippocampus and the visual cortices were observed in Alzheimer's disease (AD) and abnormal bilateral fronto-parietal, fronto-cingulate, and fronto-thalamic connectivity were observed in schizophrenia patients during the resting-state, which indicated reduced integrity and efficiency of disease related networks [9,30]. These findings may be beneficial for understanding disease states, as well as providing potential diagnostic information and treatment strategies. All of these studies suggest that resting-state fMRI might be an appropriate approach for studying heroin addiction. Although Liu et al. [20] and Ma et al. [21] reported addiction-related alteration in resting-state brain connectivity, it is unclear whether these resting-state connectivity alterations were associated with chronic heroin use [31].

To systematically investigate abnormal resting-state characteristics during the resting-state in heroin-dependent individuals, a novel approach to analyze complex systems, defined as the graph theory analysis (GTA), was applied to detect a sophisticated brain functional connection during resting-state within the heroin-dependent group and the control group, which thoroughly assesses the topological properties of networks by evaluating the strength, temporal and spatial patterns of interactions in the brain and is suitable to detect disruption in diseases-related networks [3,19,20]. To identify the relationship between chronic heroin use and features of the resting network, correlation analyses between statistical parameters (the degree: D and shortest absolute path length: L) and duration of heroin use were further carried out in heroin-dependent individuals. We hypothesized that topological properties of the brain network during resting-state in heroin-dependent individuals would be disrupted and these disruptions probably occurred in brain regions associated with drug-related functional circuits and stress regulation. More importantly, these abnormal resting-state topological properties would correlate with duration of heroin use.

The experimental protocol was approved by the Institutional Review Board of The Fourth Military University, China. Due to the limitations of data collection, 11 abstinent heroin-dependent patients (right-handed males, age 37.2 ± 7.3 years, range 25–47 years) were enrolled from a local methadone replacement therapy center. They were screened by the Structured Clinical Interview (SCID-IV) for the Statistical Manual of Mental Disorders to confirm the diagnosis of opiate dependence according to the criteria set forth in the DSM-IV (Fourth Edition). Exclusion criteria included psychiatric, neurological, and medical disorders requiring immediate treatment; additional current substance abuse/dependence diagnosis; and contraindications to being scanned. All heroin-dependent subjects had a mean heroin dependence history of 89.5 ± 55.7 months (range 19–182 months), a daily heroin consumption of 0.6 ± 0.3 g (range 0.2–1.5 g), mean abstinence from heroin around 4.9 ± 0.8 months (range 3–6 months) and had a negative test for the presence of morphine in the urine analysis (reagent produced by China Carrie City International Engineering Co.). None of the patients had a history of neurological illness or injury with the exception of drug addiction. No patients displayed overt behavioral signs of heroin intoxication.

11 age-, education- and gender-matched healthy right-handed individuals (male, age 36.8 ± 7.4 years, range 26–51 years) were recruited from the local community. None of the subjects was taking prescription drugs that affected the central nervous system within 1 week of testing and had a history of neurological illness. None of the subjects was previously exposed to a high magnetic field. All subjects were fully informed of the nature of research and gave written consent. Information about the demographic and clinical information of heroin-dependent individuals and controls is presented in Table 1.

Table 1
Demographic and clinical characteristics of heroin-dependent and control subjects (mean ± SD).

	Control subjects	Heroin-dependent subjects
Age (years)	36.8 ± 7.4	37.2 ± 7.3
Education (years)	9.1 ± 3.2	9.8 ± 2.5
Duration of heroin use (months)	N/A	89.5 ± 55.7
Dosage of heroin use (g/day)	N/A	0.6 ± 0.3
Duration of abstinence from heroin (months)	N/A	4.9 ± 0.8
Methadone dose on the day of the scanning (mg)	N/A	34.2 ± 18.7

This experiment was carried out in a 3T GE scanner. Prior to the functional run, a high-resolution structural image for each subject was acquired using three-dimensional MRI sequences with a voxel size of 1 mm^3 using an axial Fast Spoiled Gradient Recalled (3D-FSGPR) (TR 500 ms; TE 7.7 ms; matrix 256×256; field of view 220 mm × 220 mm; 25 slices, 4 mm thickness, 1 mm inter-slice gap). 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°) was acquired. About 150 echo-planar volumes were acquired during the resting scan, and functional imaging scanning lasted for 5 min. Subjects were instructed to keep their eyes closed, not to think about anything, and to stay awake during the entire scan. After scanning, all subjects reported that they stayed awake during the entire scan.

The preprocessing steps were performed according to our previous publication [20] in SPM5 (http://www.fil.ion.ucl.ac.uk/spm/). A key issue in characterizing the brain topological network is the construction of the functional connection matrix. For comprehensively characterizing the topological properties of brain networks, we down-sampled the whole brain to 6 mm isotropic voxels and obtained 3446 regions of interest (ROI). For each subject, the mean time course of each ROI was correlated with the others in the whole brain. Finally, a $n \times n$ matrix of Pearson's correlation coefficients was calculated between all voxel-pairs ($n = 3446$) for all participants. From the correlation coefficients matrix, we compared the threshold ($\bar{r}_{\text{thre}}$) with the correlation coefficient (r_{ij}). Each statistically significant connection could be represented as an undirected edge if r_{ij} exceeded $\bar{r}_{\text{thre}}$ and the edges between ROIs made up the whole brain functional network. To obtain better normality of the correlation coefficients, Fisher's r-to-z transformation was employed, and finally an unweighted and undirected binary graph was created for each subject.

Several important parameters, i.e. D, L and clustering coefficient (C) [3,19,20], were employed to evaluate the different topological properties between heroin-dependent individuals and the control subjects. In graph theory, the D of a node of the graph is the number of edges incident to the node and this most fundamental network index can be used as a measurement of the intensity of functional connectivity [20]. The brain regions showing high value of D in network were considered the functional connectivity cores [3]. For the binary network, the C of a node is defined as the ratio of the number of existing connections to the number of all possible connections in the subgraph; it is a measure of the extent of local cliquishness or local efficiency of information transfer of the network. L quantifies the extent of the average connectivity or the overall routing efficiency of the network. A small-world network is characterized by a high C and a low L. The ratio $\gamma = (C_{\text{net}})/(C_{\text{rand}}) > 1$ and the ratio $\lambda = (L_{\text{net}})/(L_{\text{rand}}) \approx 1$ were evaluated in small-world networks. The ratio $\delta = (\gamma)/(\lambda)$, termed as small-world scalar, can be summarized for small-world networks as typically being >1. Small-world networks are attractive models for connectivity of nervous systems characterized by the combination of high clustering and short path

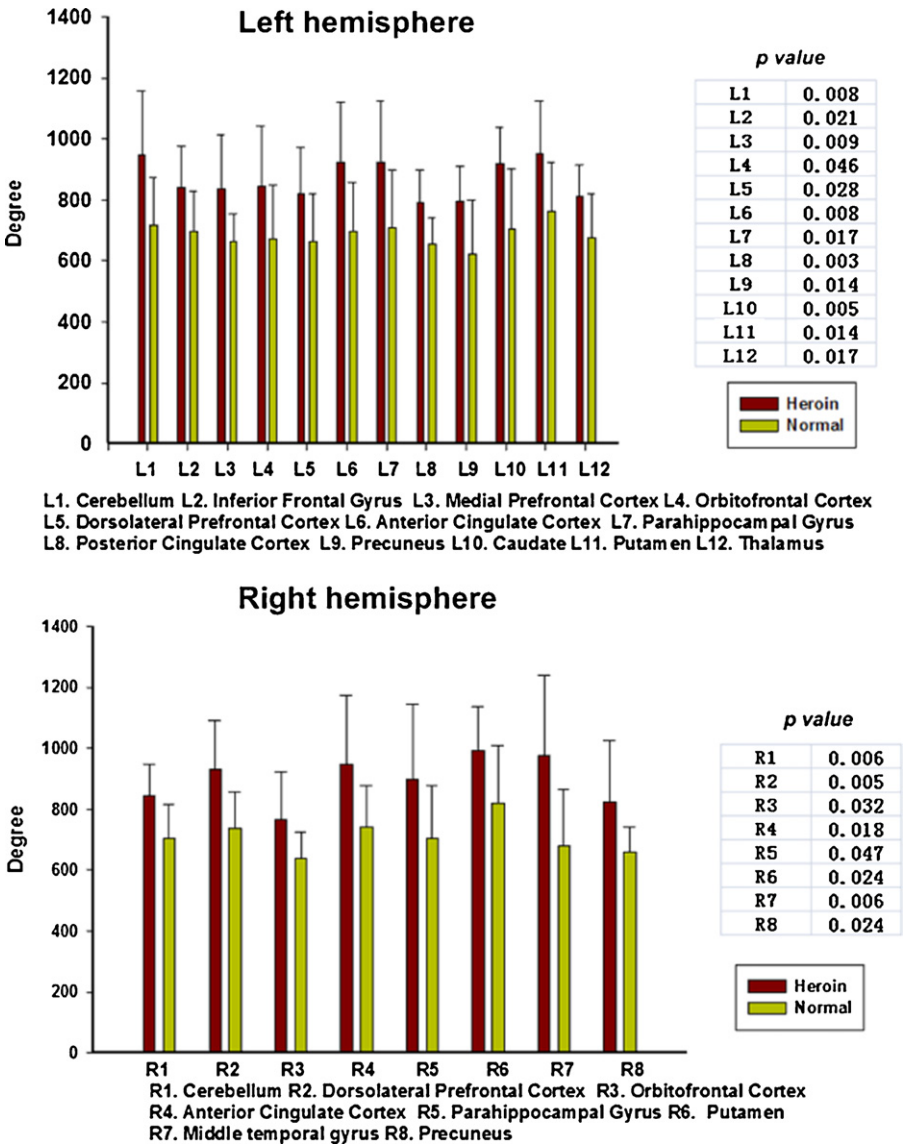

Fig. 1. Comparison of the D of differences between chronic heroin users and control subjects and corresponding peak p values (two sample t-test).

length, which confers a capability for both specialized or modular processing in local neighborhoods and distributed or integrated processing over the entire network [20]. All these parameters were compared among heroin-dependent patients and control group and Bonferroni correction was applied for the multiple comparisons. For visualization, the map of D differences was standardized by the transformation given as follows:

$$z_i = \frac{D_i - \overline{D}}{\sigma_D}, i = 1 \ldots n$$

where D_i is the D of region i, $\overline{D}$ is the mean D across all of the regions, σ_D is the SD of the D of all of the regions, and n is the number of regions across the whole brain. In the heroin-dependent group, partial correlations were employed to calculate the correlation coefficient between D and L of the regions showed significantly different topological properties among the two groups and the duration of heroin use, including age, education and duration of abstinence from heroin use as the covariates in the in-house program.

The networks of these two groups were created under the same threshold. For the control group, $L_{control} = 3.00$ and $C_{control} = 0.40$. Compared with the random networks corresponding to the number of nodes, mean D and D distribution, the network of control subjects had an almost identical path length ($\lambda_{control} = 1.15$), but was more locally clustered ($\gamma_{control} = 33.35$), resulting in a small-world scalar of $\delta_{control} = \gamma_{control}/\lambda_{control} = 29.00$, $L_{heroin} = 3.00$ and $C_{heroin} = 0.37$. Compared with the random networks, the network of control subjects had an almost identical path length ($\lambda_{heroin} = 1.20$), but was more locally clustered ($\gamma_{heroin} = 28.46$), resulting in a small-world scalar of $\delta_{heroin} = \gamma_{heroin}/\lambda_{heroin} = 23.72$. Relative to the control group, the small-world scalar was smaller in the heroin-dependent group.

Our results demonstrated that compared with the control group, D were higher in the OFC, dorsolateral prefrontal cortex (DLPFC), rostral ACC (rACC), precuneus, parahippocampal gyrus, putamen and cerebellum bilaterally; the inferior frontal cortex, medial prefrontal cortex (MPFC), caudate, thalamus, and posterior cingulate cortex (PCC) in the left cerebrum; and finally, the right middle temporal gyrus in heroin-dependent patients (Fig. 1).

The correlation analysis showed that the duration of heroin use was positively correlated with the D of the right parahippocampal gyrus, left putamen and bilateral cerebellum, but negatively correlated with the parameter L in the same regions ($p < 0.05$) (Fig. 2).

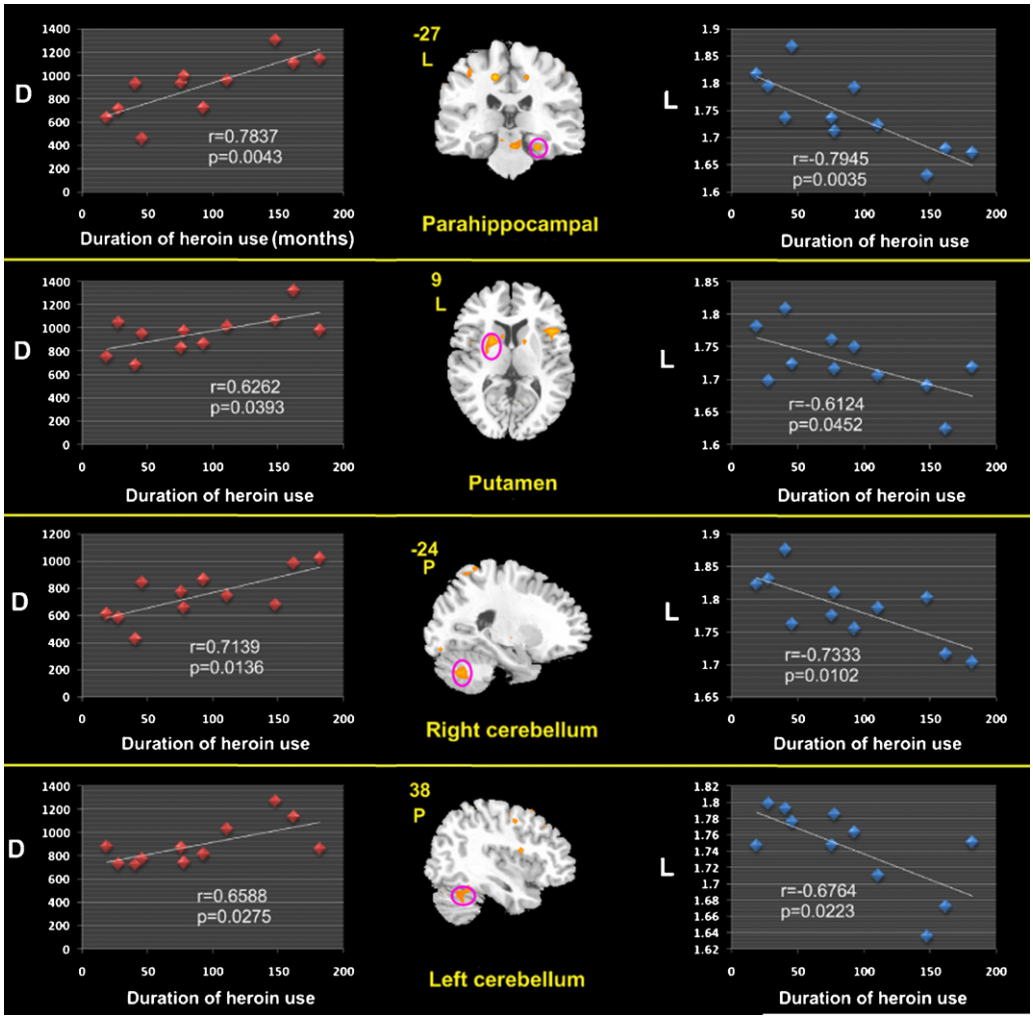

Fig. 2. Correlation maps between duration of heroin use and topological properties (*D* and *L*) of brain regions (*r*: correlation coefficient; *p*: *p* value).

Although previous heroin studies indicated that drug addiction is a disorder involving many circuit impairments in reward, motivation/drive, memory, control and stress regulation [18,29], most of them adopted task-related methods and focused on one specific circuit. To systematically investigate abnormal resting-state characteristics in heroin-dependent individuals, we employed the GTA method. In general, the small-world scalar was smaller in the heroin-dependent group than in the control group, which may indicate that the topological properties of the heroin-dependent individuals' network are distorted. The *D* of several brain regions was higher in heroin-dependent patients which anchor heroin addiction-related circuits: the caudate and putamen, reward circuit; OFC and DLPFC, motivation/drive circuit; parahippocampal gyrus, memory circuit; rACC, control circuit; and the MPFC, stress regulation and emotion modulation [18,29]. The abnormal topological properties in these brain regions seen among heroin-dependent individuals can provide insights into heroin addiction.

Volkow et al. suggested four circuits involved in drug addiction, i.e. motivation/drive, memory/learning, control circuits, and reward circuits [29]. In our study, we found reward circuit abnormalities by demonstrating that the caudate and putamen, major parts of the striatum, had higher *D* in the heroin-dependent network compared with the control group. Previous studies had noticed that drugs of abuse increase the extracellular concentration of DA in the striatum (where the NAc is located) and that these increases were associated with their reinforcing effects [24,29]. A significant difference in *D* of the OFC (motivation/drive circuit) and DLPFC within the two groups was also observed. The DLPFC, which integrates cognitive and motivational information from the OFC and other regions, contributes to regulatory processing [15]. In addition, other studies referring to the disruption of the OFC and DLPFC in drug users have provided evidence for the OFC and DLPFC's roles in motivation-relevant processes [11,12]. We also detected that the *D* of the parahippocampal gyrus (memory/learning circuit) was higher in heroin-dependent patients. The parahippocampal gyrus, a grey matter cortical region of the brain that surrounds the hippocampus, plays an important role in memory encoding and retrieval [1]. Memory is likely to influence the effects of the drug during intoxication, since it sets the expectations of the drug's effects in drug- dependent subjects [25,29]. Many factors, such as a place, a person or a cue can trigger an intense desire for the drug [10,25]. Previous heroin studies had reported hypoactivation of the rACC (control circuit) in a GO/NOGO task in heroin users [8] and cocaine users [16], which indicated that the rACC plays an important role in inhibitory control. Our results showed a higher D of the rACC in heroin-dependent patients compared with the control group, which was possibly associated with former studies [8].

Stress has been consistently shown to increase drug craving, relapse and compulsive drug seeking in drug-dependent individuals [5,28]. Several studies have shown that acute stress exposure increases dopamine release in the striatum [24,29] and MPFC (including the ACC) and the PCC which are involved in emotion regulation and stress-induced drug craving. These are known to increase the risk of relapse [17,18]. Our results revealed a higher *D* of the MPFC, ACC, PCC, putamen and caudate (major parts of the striatum) in heroin-dependent patients, and these abnormalities may be related with functional deficits in stress regulation that finally leads to drug addiction [18,28].

These observations of abnormal resting-state characteristics in heroin-dependent individuals suggested abnormal functional organization in the addicted brain and provided insights into heroin addiction. Unfortunately, these findings failed to answer whether or not these resting-state connectivity alterations were associated with chronic heroin use [31].

Another important finding in the present study is the relationship between chronic drug use and the network properties of several brain regions. Significantly positive correlations were observed between duration of heroin use and the *D* of the bilateral cerebellum, right parahippocampal gyrus and left putamen, and significantly negative correlations were seen between the duration of heroin use and the *L* of these regions, even after including other confounding factors, such as age, education and duration of abstinence from heroin use. The correlation between duration of heroin use and topological properties (*D* and *L*) of some brain regions (bilateral cerebellum, right parahippocampal gyrus and left putamen) in abstinent heroin-dependent patients suggests that heroin use has a cumulative effect; the longer the heroin use, the higher the *D* in the putamen and parahippocampal gyrus, and the longer the heroin use, the smaller the corresponding *L* in heroin-dependent individuals. This interesting result suggested that as the heroin use persisted, the information transfer of reward and memory circuits became more complicated and probably led to poor control and decision-making. This is in agreement with a previous behavioral study showing a negative correlation between duration of heroin use and performance in a stop-signal task [23]. Early intervention is particularly important for the treatment of heroin addiction. Besides, more work is needed to provide a more specific and definitive interpretation of the results in the present study, e.g. the role of the cerebellum in heroin addiction.

Several limitations should be considered when interpreting the existing results. First, the sample size is small in this study (11 heroin-dependent subjects). Further studies will be conducted with a larger population. Second, while methadone is commonly abused [13], we cannot rule out methadone maintenance treatment (MMT) effects. Subjects were MMT patients for about 5 months. Future studies are recommended to assess such effects by comparing short-term MMT patients with long-term MMT patients.

In conclusion, the current study systematically investigated abnormal resting-state characteristics during the resting-state in heroin-dependent individuals and assessed the relationship between these resting-state connectivity alterations and duration of heroin use. Hopefully our findings will shed light on the mechanisms underlying opiate addiction.

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