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Disrupted Default Mode Network and Basal Craving in Male Heroin-Dependent Individuals: A Resting-State fMRI Study

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ABSTRACT

Background: Craving is associated with a high probability of relapse. However, the relationship between functional connectivity in the default mode network (DMN) during resting state and basal craving of heroin-dependent individuals remains unknown.

Methods: Data used in the present study were collected between August 10, 2009, and June 28, 2011. Twenty-four male heroin-dependent individuals based on *DSM-IV* criteria and 20 male healthy control subjects participated in a study of resting-state functional magnetic resonance imaging. The basal heroin craving of the heroin-dependent group was evaluated. The DMN networks were identified by group independent component analysis. The between-group difference in functional connectivity was analyzed, and the relationship between functional connectivity in the DMN and basal heroin craving in the heroin-dependent group was also analyzed.

Results: In all subjects, 2 spatially independent default mode subnetworks were identified: the anterior and posterior subnetworks. The anterior subnetwork, mainly the dorsal medial prefrontal cortex, showed decreased functional connectivity in the heroin-dependent group relative to the healthy control group ($P < .05$, familywise error corrected). However, the functional connectivity in dorsal medial prefrontal cortex was negatively correlated with the basal craving of the heroin group ($P = .01$, $r = -0.50$). No significant difference in the functional connectivity of the posterior subnetwork was found.

Conclusions: Our findings suggest that abnormal functional connectivity within the anterior subnetwork of DMN in heroin-dependent individuals is associated with basal heroin craving, and it may serve as neural underpinnings for the mechanism of heroin addiction.

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Heroin addiction has become an increasingly serious problem in China in recent years.[1,2] Such addiction is characterized by the failure to resist one's impulses to seek and take drugs despite serious and negative consequences.[3] Task-related neuroimaging studies[4–6] have shown an abnormal functional organization of brains in addicted populations, in which there is enhanced salience of drug-related cues but weakened strength of cognitive control. Drug-related cues-induced[7–11] or stress-induced[12–14] craving is known to play a key role in relapse among drug addicts. On the other hand, basal heroin craving represents a baseline internal urge for heroin without influence from external stimuli. Given the neural-plastic adaptations as a result of long-term heroin exposure, the function of substrates associated with craving should be altered to some extent. However, the relationship between basal craving and basal functional connectivity of the brain without the influence of drug-related cues in heroin-dependent individuals remains unknown.

The default mode network (DMN) has been identified during resting state.[15] It mainly comprises brain regions including the medial prefrontal cortex (MPFC), anterior cingulate cortex (ACC), precuneus, posterior cingulate cortex (PCC), and medial, lateral, and inferior parietal cortex. This network is suggested to be involved in self-referential processes such as the processing of internal states[15] and to be deactivated when engaging in various behavioral tasks or when responding to the environment.[16] The brain regions (MPFC,[9,16,17] ACC,[7,9,12,17–22] and PCC[20,23,24]) within DMN are generally identified in different drug-cue response tasks. Also these regions have been identified in resting-state functional magnetic resonance imaging (fMRI) studies in heroin addiction.[25–36] Specifically, Ma et al[37] found that the heroin-dependent individuals demonstrated decreased functional connectivity in dorsal anterior cingulate cortex and caudate in the DMN when compared with the healthy controls. Another study[33] demonstrated decreased functional connectivity between the MPFC and PCC/precuneus in heroin-dependent individuals. Denier et al[35] showed that, in heroin-dependent individuals, low gray matter volume is positively associated with low perfusion within frontal regions including regions of DMN. Wang et al[34] found a decreased positive correlation between DMN and visual networks and a decreased negative correlation between DMN and task-positive networks. Therefore, the DMN is generally involved in heroin addiction. In addition, as an important part of DMN, the MPFC is suggested to be

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Clinical Points

- The default mode network (DMN) is involved in cue-induced craving in heroin-dependent patients. However, the relationship between function of DMN during resting state and basal craving for heroin remains unknown.
- For heroin-dependent patients, assessing resting-state functional connectivity in the anterior subnetwork of DMN prior to therapy initiation may help identify an indicator of relapse potential.

involved in craving processes.[17] The compulsion to use drugs is known to be frequently driven by craving. The exact relationship between functional connectivity in the DMN and basal craving for heroin remains unknown and is worthy of exploration. Examination of this relationship may be beneficial to the understanding of the intrinsic mechanism of heroin addiction from another perspective, that is, baseline characteristics.

The aim of our study was to assess the characteristics of functional connectivity in DMN during resting state in heroin-dependent individuals and to assess the relationship between the functional connectivity in the DMN and basal subjective heroin craving.

It has been demonstrated that the DMN could be decomposed into a spatially anterior subnetwork (eg, MPFC and anterior cingulate cortex) and posterior subnetwork (eg, PCC, precuneus, and bilateral inferior parietal lobe).[38,39] Given the suggestion that the anterior part of DMN is mostly involved in heroin addiction and craving processes during drug-cue response task,[40,41] we hypothesized that the heroin-dependent individuals are characterized by decreased functional connectivity in DMN, especially the anterior part of DMN. Specifically, we hypothesized that the decreased functional connectivity could be negatively correlated with the basal subjective heroin craving.

METHODS

Participants

Data used in the present study were collected between August 10, 2009, and June 28, 2011. Forty-seven subjects participated in this study, including 27 heroin-dependent individuals (aged from 23 to 44 years, education from 6 to 17 years) and 20 healthy control volunteers (aged from 19 to 46 years, education from 6 to 14 years). All participants were male smokers. Subjects completed a clinical interview prior to inclusion in the study. Inclusion criteria for the heroin-dependent group were (1) *DSM-IV* criteria for heroin dependence for at least 1 year without use of any other opioid such as methadone and buprenorphine, (2) right-handed, (3) aged 18–50 years, (4) completion of detoxification treatment with no somatic symptoms of withdrawal, and (5) negative morphine urinalysis tests. Exclusion criteria for all participants were (1) current or past psychiatric illness other than heroin and nicotine dependence, (2) history of head trauma, (3) neurologic signs or history of neurologic disease, (4) current medical illness or recent medicine use, (5) presence of magnetically active objects in the body, and (6) claustrophobia or any other medical condition that would preclude the subject from undergoing MRI scan for approximately 40 minutes.

All aspects of the research protocol were reviewed and approved by the ethics committee of Tangdu Hospital, Xi'an, China, and comply with the Helsinki Declaration of 1975, as revised in 2008. Written informed consent was given by each subject. The experiment methods were carried out in accordance with the approved guidelines.

Experimental Paradigm

Participants underwent a resting-state fMRI scan. Prior to the scan, the basal heroin craving was assessed by a 0–10 visual analog scale[11] from each heroin-dependent individual. The question, "To what extent do you feel the urge to use heroin?" was asked to get heroin craving ratings (0 for the least craving and 10 for the strongest craving).

MRI Data Acquisition

Scanning took place on the 3.0T GE Signa Excite HD scanner (GE Healthcare) at Tangdu Hospital. Prior to formal experimental scanning, subjects underwent "mock scans" for 1 minute in order to become familiar with the scanning environment. The formal scanning began with a 10-second dummy scan followed by the data acquisition. During the formal scanning, each subject was instructed to keep still, rest with his eyes passively viewing the white cross hair with black background projected in the center of the mirror mounted on the head coil, and refrain from thinking about anything special. Ear plugs and foam padding were used to reduce noise and minimize head movement. The functional images were collected using a gradient echo planar imaging sequence (repetition time = 2,000 milliseconds, echo time = 30 milliseconds, field of view = 256 × 256 mm^2, imaging matrix = 64 × 64, number of slices = 32, slice thickness = 4 mm, gap = 0 mm, flip angle = 90°, spatial resolution = 4 × 4 × 4 mm^3). For each subject, 150 echo planar volumes were collected respectively during the resting-state fMRI scan. The total acquisition duration lasted for 5 minutes 10 seconds. The corresponding high-resolution 3D, T1-weighted images were also collected for use for spatial normalization of the data sets to a standard atlas. The fast spoiled gradient echo sequence was used (repetition time = 7.8 milliseconds, echo time = 3.0 milliseconds, field of view = 256 × 256 mm^2, imaging matrix = 256 × 256, number of slices = 166, slice thickness = 1 mm, spatial resolution = 1 × 1 × 1 mm^3). The structural data were checked by an experienced radiologist to identify whether there were structural abnormalities.

Data Preprocessing

The imaging data analysis was performed with SPM8 software (http://www.fil.ion.ucl.ac.uk/spm) and Data Processing Assistant for Resting-State fMRI (DPARSF) software.[42] The fMRI images were slice-time and motion corrected; registered to the fast spoiled gradient echo 3D, T1-weighted images; and then normalized to a standard

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SPM T1 template. The images were resampled to 3-mm isotropic voxels, and spatially smoothed (Gaussian filter of the 6-mm kernel). Participants with excessive head motion (more than 1.5 mm in translation or 1.5 degree in rotation) were excluded from the analysis. Of the 47 subjects who completed the MRI scan, 3 heroin-dependent subjects were excluded because of excess head motion. Therefore, data from 24 heroin-dependent subjects and 20 healthy control subjects were included in the analyses (Table 1).

Table 1. Demographic and Clinical Characteristics of Subjects

Characteristic	Heroin Dependent (n = 24), Mean ± SD	Healthy Control (n = 20), Mean ± SD	*t* Value	*P* Value
Age, y	32.8 ± 6.6	35.0 ± 7.0	−1.142	.263
Education, y	10.9 ± 3.1	10.1 ± 2.3	0.984	.318
No. of cigarettes/d	17.8 ± 5.9	15.0 ± 5.0	1.820	.080
Duration of heroin use, mo	78.6 ± 50.1	…	…	…
Heroin dose, g/d	1.0 ± 1.2	…	…	…
Total heroin dose used, g	2,171.1 ± 2,484.9	…	…	…
Duration of abstinence, d	21.7 ± 16.0	…	…	…

Group Independent Component Analysis

All the preprocessed imaging data were then analyzed with the GIFT software (http://icatb.sourceforge.net/). Group independent component analysis was performed to decompose the resting-state imaging data into spatially independent components.

Although methods of how to choose the optimal number of components are in development, there is no consensus on it so far. We set the number of components at 20 based on recent resting-state fMRI studies.[37,43,44] For each participant, 20 spatially independent components were identified using group independent component analysis. Then, DMN components were identified using a DMN template based on previous studies.[44,45] We used the WFU PickAtlasTool (version 2.4; http://fmri.wfubmc.edu/software/PickAtlas) to create the DMN template. The bilateral precuneus, posterior cingulate, angular, and superior medial frontal cortex were included in the template. A multiple regression was conducted in a voxelwise manner, and components (subnetworks) that best fit the DMN template were selected.[46] The amplitude of each component reflects the contribution of each region to distributed and coherent activity within that component (ie, functional connectivity). Subsequently, subject-specific independent components were entered into second-level analyses. Voxelwise 1-sample *t* tests ($P < .001$, uncorrected) were employed to obtain the spatial pattern of the DMN in the 2 groups. Moreover, 2-sample *t* tests ($P < .05$, familywise error corrected) were performed to compare subject-specific DMN components between the 2 groups. Finally, we extracted the amplitude of the differential DMN regions between the 2 groups and calculated the correlations between functional connectivity strength and basal craving scores within the heroin-dependent group. The significance was set at $P < .05$. All coordinates reported were in the Montreal Neurological Institute space.

RESULTS

Demographic and Psychometric Characteristics

The heroin-dependent and healthy control groups did not show significant difference in age, years of education, and cigarettes smoked per day (Table 1). For the heroin-dependent group, the mean ± SD basal craving score was 2.5 ± 1.7 (range, 0.1–7.0).

Imaging

Two independent components had very close correlations with the DMN template, and their correlations were far above that of others (see Supplementary eTable 1). This result suggests that both of these subcomponent networks could be candidates for the DMN components. Moreover, both of these 2 subcomponent networks included only part of the DMN regions. When we combined these 2 subcomponent networks, the new network was very similar to the DMN template. Given this situation, we decided to use 2 subcomponent networks as some researchers have done.[44,45] The 2 subnetworks of the DMN were identified in participants as an anterior subnetwork and a posterior subnetwork. The anterior subnetwork had the highest intensity in MPFC, and the posterior subnetwork had the highest intensity in the PCC and bilateral precuneus. The 2 subnetworks were spatially independent from each other, and the time series were asynchronous in these 2 subnetworks. The spatial patterns of the anterior and posterior subnetworks of the 2 groups are shown in Figures 1 and 2 (1-sample *t* test, $P < .001$). It can be seen that the 2 groups had similar expressions of the DMN subnetworks.

Compared with the healthy control group, the heroin-dependent group demonstrated significantly decreased functional connectivity in the dorsal MPFC (Brodmann area 9; peak $t = -10.8$; coordinates x = −3, y = 63, z = 30; number of voxels = 43), which was mainly involved in the anterior subnetwork of DMN (Figure 3). No significantly increased functional connectivity of the anterior DMN was found in the heroin-dependent group relative to the healthy control group. No significant difference in functional connectivity in posterior DMN between the 2 groups was found.

Correlation

For the heroin-dependent group, the functional connectivity in dorsal MPFC was negatively correlated with the basal craving ($r = -0.50$, $P = .01$) (Figure 4).

DISCUSSION

To our knowledge, this neuroimaging study is the first to assess the relationship between the characteristics of functional connectivity in DMN and basal craving in heroin addiction. As we hypothesized, the present findings demonstrated that the heroin-dependent group was featured by decreased functional connectivity mainly in the dorsal MPFC within the anterior DMN, and the

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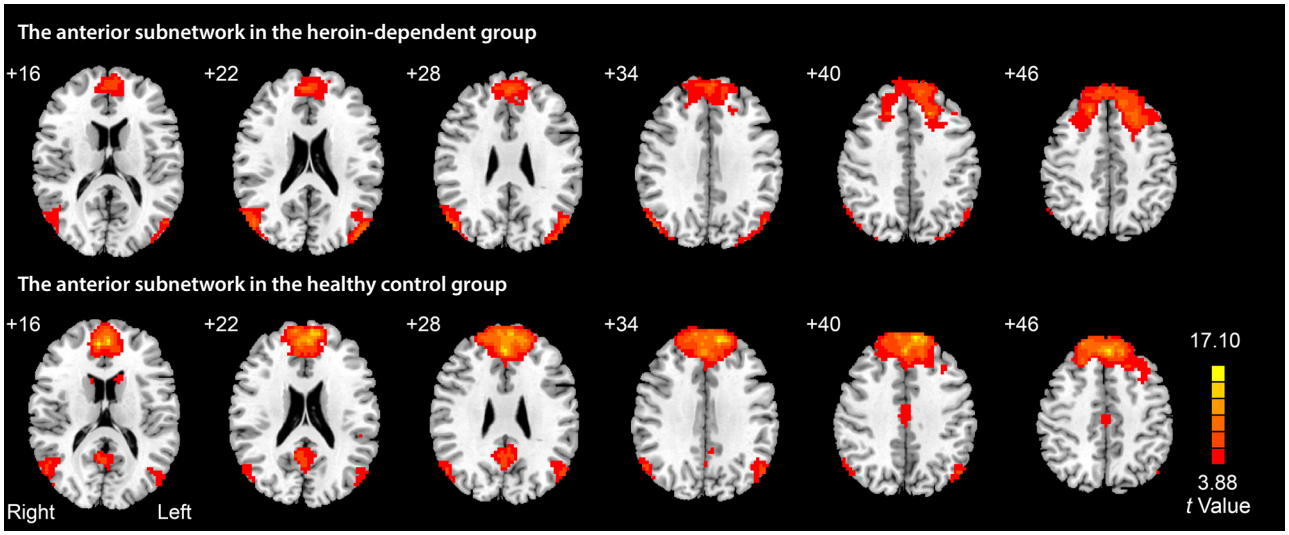
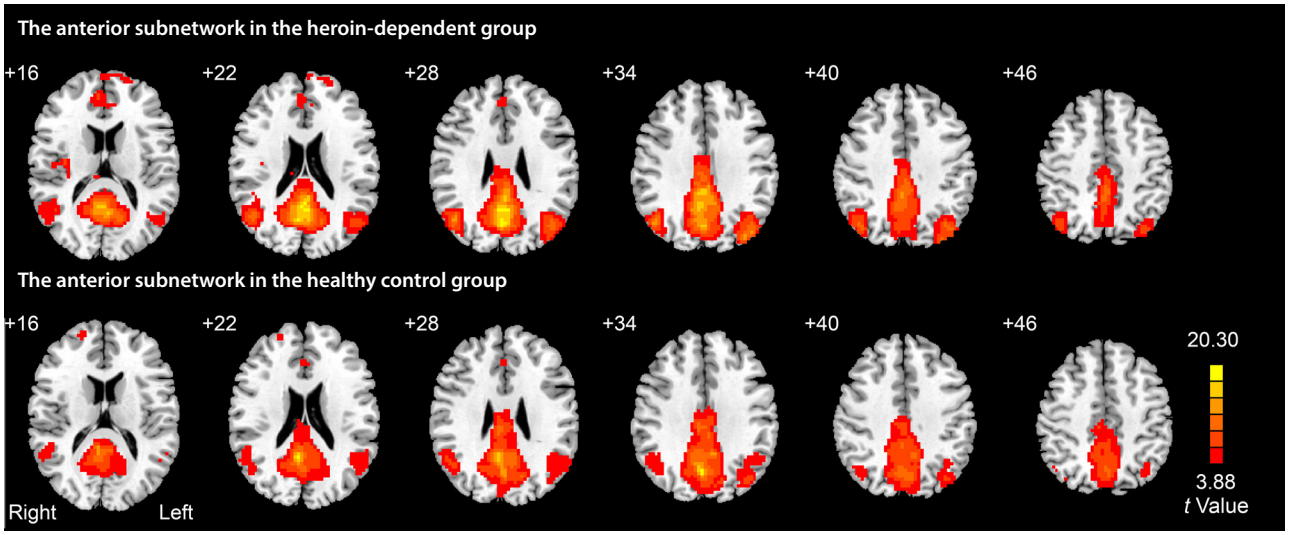
Figure 1. Spatial Map of the Anterior Subnetwork of the Default Mode Network in the Heroin-Dependent and Healthy Control Groups[a]



[a]The statistical parametric maps are based on 1-sample *t* tests against 0 at each voxel ($P < .001$, uncorrected).

Figure 2. Spatial Map of the Posterior Subnetwork of the Default Mode Network in the Heroin-Dependent and Healthy Control Groups[a]



[a]The statistical parametric maps are based upon 1-sample *t* tests against 0 at each voxel ($P < .001$, uncorrected).

functional connectivity in dorsal MPFC was negatively correlated with basal subjective craving for heroin.

The DMN is believed to be related to attention and self-referential and introspective thoughts and plays a key role in evaluating information from external and internal environment in the resting state.[47] As an important part of the DMN, the MPFC integrates both emotional and cognitive information and functions as a mediator of frontolimbic circuit regulation.[48,49] The dorsal MPFC has dense connectivity with a number of key regions involved in addiction such as the nucleus accumbens, amygdala, and monoaminergic brainstem nuclei. A growing body of literature points to the dorsal MPFC as a key structure involved in drug addiction. Drug cue reactivity studies[19,20] have consistently demonstrated that the dorsal MPFC is one of the brain regions that increases activation in response to drug-related cues. In addition, it was suggested that the cue reactivity in the dorsal MPFC is related to treatment outcome and risk of relapse.[50] The preclinical studies of cocaine addiction also demonstrate that when the dorsal MPFC activity is dominated by cue response processes, decreased response of dorsal MPFC reduces cocaine seeking

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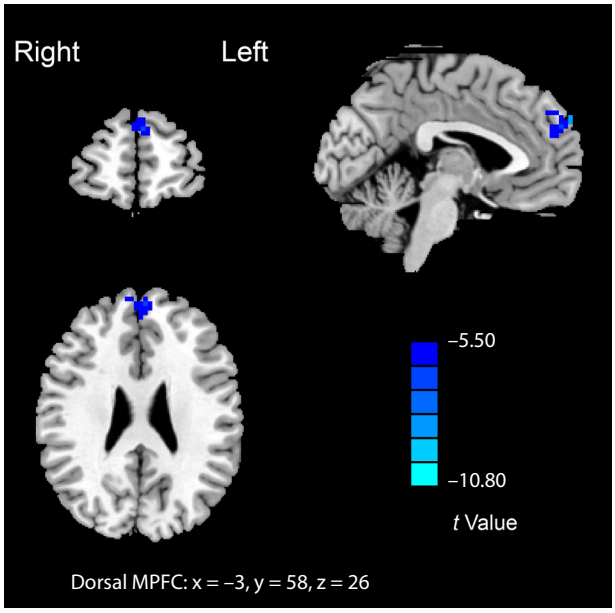
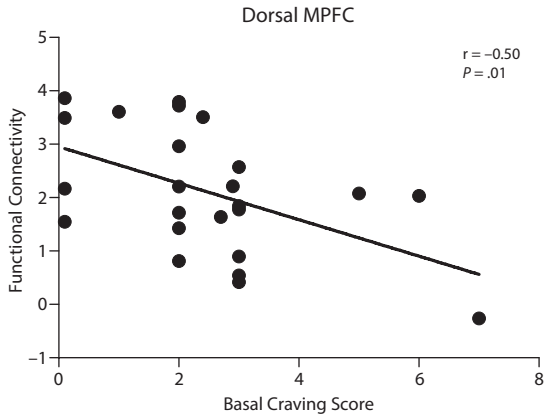
Figure 3. Difference in Functional Connectivity Within the Anterior Subnetwork of Default Mode Network Between Heroin Group and Healthy Control Group[a]



[a]$P < .05$, familywise error corrected.
Abbreviation: MPFC = medial prefrontal cortex.

Figure 4. Correlation Map Between Functional Connectivity of the Medial Prefrontal Cortex and the Baseline Craving of Heroin-Dependent Individuals



Abbreviation: MPFC = medial prefrontal cortex.

and relapse vulnerability,[51–53] whereas increased response of dorsal MPFC enhances cocaine seeking and relapse vulnerability.[54] An animal study by George et al[55] suggested that the dysregulation of MPFC (including dorsal MPFC) interneurons may be an early index of neuroadaptation in alcohol dependence. Further, another animal study by Lu et al[56] demonstrated that fMRI response in the MPFC (including dorsal MPFC) predicts cocaine self-administration history.

In our findings, the decreased resting-state functional connectivity in the anterior subnetwork of DMN mainly including dorsal MPFC in the heroin group relative to healthy group may suggest abnormal regulated awareness of internal state. The dorsal MPFC is densely innervated by dopaminergic fibers from the ventral tegmental area and substantia nigra,[54] and it has high level of expression of dopamine transporters. Neuroimaging studies have showed that drug abusers are featured by significant decreases in dopamine D_2 receptors and in dopamine release. This abnormal dopamine function is associated with reduced regional activity in prefrontal regions.[57] Fox and colleagues[58] certificated that the human brain is intrinsically organized into dynamic and anticorrelated functional networks, such as cognitive control network and DMN. There is also evidence that dopamine facilitates the deactivation DMN during an emotion recognition task.[59] Thus, conversely, the hypoactivity in the dorsal MPFC of heroin-dependent individuals during a resting state is consistent with a decrease in dopamine neurotransmission in heroin addiction.

Interestingly, the connectivity in the dorsal MPFC of the heroin group was negatively correlated with the subjects' basal craving score for heroin. As dopamine cells fire in response to salient stimuli and facilitate conditioned learning, the activation by drugs will be experienced as highly salient, which results in driving motivation to take the drug and further strengthens conditioned learning and produces compulsive behaviors.[57] Long-term repeated drug abuse decreases dopamine D_2 receptors and dopamine release in the brain, and it may raise the thresholds required for dopamine cell activation and signaling, which in turn result in craving for drugs. On the basis of previous studies and our findings, we postulated that the decreased connectivity in the anterior subnetwork of DMN during a resting state is associated with enhanced internal awareness in heroin-dependent individuals. Their increased awareness of internal states could result in greater craving response to stress or heroin-related cues and, in turn, increase the risk for relapse.

Our findings showing that the DMN decomposed into 2 independent subnetworks support previous studies[38,44] that have reported heterogeneity of the DMN. We did not find the difference in functional connectivity within the posterior subnetwork of DMN between the heroin-dependent and healthy control groups. In this regard, our result is in line with what Ma and colleagues[37] found. We speculate that the dysfunction of the anterior subnetwork of DMN may play a more important role in underpinning the mechanism of heroin addiction.

The current findings suggest that future therapies for heroin addiction should assess basal functional connectivity in the anterior subnetwork of DMN prior to treatment as an indicator of relapse potential. Furthermore, changes in basal functional connectivity in the DMN after treatment might serve as a marker of treatment efficacy. Therapies for heroin addiction that would increase the functional connectivity in the anterior subnetwork of DMN would presumably reduce the rate of relapse.

Our data should be interpreted in light of some limitations. First, this study is restricted to men because of the reality of few heroin-dependent women in the district

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where we enrolled the subjects. Therefore, whether our findings generalize to addicted female subjects awaits further investigation. Second, although all of the participants denied falling asleep during the MRI scan, the inability to control subjects' thoughts during imaging was a limitation common in resting-state fMRI studies. Third, although all of the subjects were recruited based on strict inclusion and exclusion criteria and there was no difference in cigarettes smoked per day between the heroin-dependent and healthy control groups, we could not rule out the confounding effects of use of other drugs besides heroin.

To summarize, we found that heroin-dependent individuals demonstrated decreased functional connectivity within the anterior subnetwork of DMN, and the disrupted connectivity in this subnetwork was associated with the basal heroin craving. The abnormal functional connectivity in the anterior subnetwork of DMN may serve as neural underpinnings for the mechanism of heroin addiction.

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Drug names: methadone (Methadose and others); morphine (Kadian, Morphabondand others).

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Supplementary material: See accompanying pages.

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Supplementary Material

Article Title: Disrupted Default Mode Network and Basal Craving in Male Heroin-Dependent Individuals: A Resting-State fMRI Study

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List of Supplementary Material for the article

1. eTable 1 — The correlation coefficient between the components and the default mode network template

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Supplementary table 1. The correlation coefficient between the components and the default mode network template

Order	Heroin-dependent group	Healthy control group
1	0.548	0.489
2	0.357	0.432
3	0.192	0.218
4	0.175	0.129
5	0.106	0.078
6	0.086	0.070
7	0.071	0.057
8	0.067	0.037
9	0.050	0.033
10	0.032	0.031
11	0.031	0.023
12	0.027	0.022
13	0.024	0.020
14	0.023	0.010
15	0.016	0.005
16	0.014	0.004
17	0.007	0.003
18	0.002	0.002
19	0.002	0.001
20	0.001	0.001

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