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Combining spatial and temporal information to explore resting-state networks changes in abstinent heroin-dependent individuals

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ABSTRACT

Majority of previous heroin fMRI studies focused on abnormal brain function in heroin-dependent individuals. However, few fMRI studies focused on the resting-state abnormalities in heroin-dependent individuals and assessed the relationship between the resting-state functional connectivity changes and duration of heroin use. In the present study, discrete cosine transform (DCT) was employed to explore spatial distribution of low frequency BOLD oscillations in heroin-dependent individuals and healthy subjects during resting-state; meanwhile resting-state functional connectivity analysis was used to investigate the temporal signatures of overlapping brain regions obtained in DCT analysis among these two groups. Main finding of the present study is that the default mode network (DMN) and rostral anterior cingulate cortex (rACC) network of heroin-dependent individuals were changed compared with healthy subjects. More importantly, these changes negatively correlated with duration of heroin use. These resting-state functional abnormalites in heroin-dependent individuals provided evidence for abnormal functional organization in heroin-dependent individuals, such as functional impairments in decision-making and inhibitory control.

Drug addiction is conceptualized as a syndrome of impaired response inhibition and salience attribution, characterized by compulsive drive to take drugs despite of serious negative consequences [9]. Emerging neuroimaging studies have reported structural and functional brain changes in heroin-dependent individuals [6,12,24–26]. They find that heroin-dependent individuals exhibited increased white matter intensity in the frontal area and decreased gray matter density in the bilateral prefrontal cortices and in the temporal regions compared with healthy subjects [16,17,26]. Functional impairments in heroin-dependent individuals have been also verified in performing a wealth of tasks, such as response inhibition and decision-making [6,12,25]. A distributed brain network has been linked to heroin addiction, including the amygdala, anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (DLPFC), medial prefrontal cortex (MPFC), nucleus accumbens (NAc) and insula [6,12,24–26]. Majority of previous heroin studies focused on structural deficits and abnormal function under specific task, investigating brain alterations in heroin-dependent individuals versus healthy subjects. However, far too little attention has been paid to resting-state abnormalities in heroin-dependent individuals [14,18].

Resting-state network analysis has been utilized to investigate the integration level of neural systems when no explicit task was engaged [3,4,10]. In addition, assessments of resting-state networks had been conducted in brain disorders [7,11]. The decreased connectivity between the hippocampus and the visual cortices were observed in Alzheimer's disease (AD) [11] and abnormal bilateral fronto-parietal, fronto-cingulate, and fronto-thalamic connectivity have also been observed in schizophrenia patients during the resting-state [7], which indicate reduced integrity and efficiency of disease related networks. These findings may be beneficial for understanding disease states, as well as providing potential diagnostic information and treatment strategies. All these studies suggest that resting-state fMRI might be an appropriate approach for studying heroin addiction. Recently, Ma et al. [18] and Liu et al. [14] reported abnormal resting-state functional connectivity in heroin-dependent individuals, suggesting abnormal functional organization in addicted brains. However, the authors failed to assess the relationship between the resting-state functional connectivity changes and heroin dependence.

This study aimed to investigate the resting-state networks changes in heroin-dependent individuals, combining both spatial and temporal information. In addition, we employed correlation

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Table 1
Demographic and clinical characteristics of heroin-dependent individuals and healthy subjects.

	Healthy subjects	Heroin-dependent individuals
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

analysis to assess the relationship between resting-state functional connectivity changes and duration of heroin use. Discrete cosine transform (DCT) [4] was employed to explore spatial distribution of low frequency BOLD oscillations during resting-state within heroin-dependent individuals and healthy subjects; meanwhile resting-state functional connectivity analysis was used to investigate the temporal characteristics of brain regions that exhibited similar spatial patterns in DCT analysis in heroin-dependent individuals and healthy subjects. We hypothesized that resting-state functional connectivity of heroin-dependent individuals was changed compared with healthy subjects and these changes probably correlated with duration of heroin use.

The experimental protocol was approved by Institutional Review Board of The Fourth Military University, China. Due to data limitation (few female patients in the treatment center), 11 abstinent male heroin-dependent patients (right-handed, 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, Fourth Edition (DSM-IV) to confirm the diagnosis of opiate dependence according to the criteria set forth in the DSM-IV. Exclusion criteria included psychiatric, neurological, and medical disorders requiring immediate treatment; additional current substance abuse/dependence diagnosis; and contraindications to scanning. All heroin-dependent individuals had a mean heroin dependence history of 89.5 ± 55.7 months (range 19–182 months), daily heroin consumption was 0.6 ± 0.3 g (range 0.2–1.5 g), mean abstinence from heroin of 4.9 ± 0.8 months (range 3–6 months) and negative test for the presence of morphine in urine-analysis (reagent box produced by China Carrie City International Engineering Co.). The patients were in good physical health and no patients displayed overt behavioral signs of heroin intoxication.

13 age-, education- and gender-matched ($p > 0.05$) healthy right-handed male individuals (male, age 36.8 ± 7.4 years, range 26–51 years) were recruited from the local community. None of the subjects were taking prescription drugs within 1 week that affected the central nervous system and had a history of neurological illness. None of the subjects were previously exposed to a high magnetic field. All subjects were fully informed of the nature of the research and had given written consent. Information about the demographic and clinical information of the heroin-dependent individuals and healthy subjects is presented in Table 1.

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°) were acquired. 150 echo-planar volumes were acquired during the rest scanning 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 scanning. After scanning, all subjects reported that they all stayed awake during the entire scanning.

The preprocessing steps were performed in Statistical Parametric Mapping – 5 (SPM5) (http://www.fil.ion.ucl.ac.uk/spm). For each subject, all functional images were realigned to the first volume. Translation and rotation were checked and images with head movements greater than 1 mm in any direction or head rotations greater than 1° were discarded. All realigned images were spatially normalized to the MNI echo-planar imaging template in SPM5, and each voxel was resampled to 2 mm × 2 mm × 2 mm. The normalized datasets were then filtered by using a bandpass filter (0.01–0.1 Hz). The normalized data set was smoothed with a 12-mm full width at half maximum (FWHM) Gaussian kernel.

The DCT analysis was followed by steps depicted in Fransson's study [4]. The discrete cosine bias set contained 60 regressors spanning the frequency of 0.01–0.1 Hz. Statistical parametrical maps

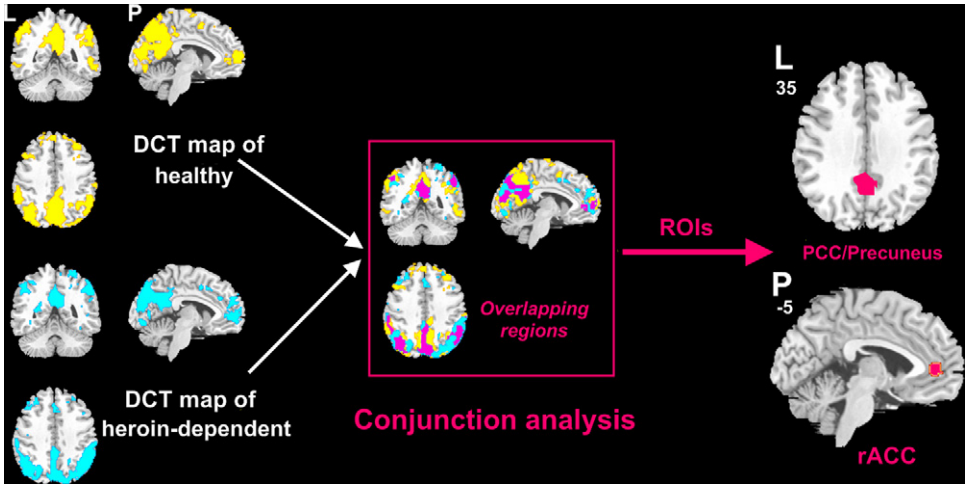

Fig. 1. DCT analysis result. We chose our ROIs (PCC/Precuneus and rACC) from the overlapping regions of heroin-dependent individuals and healthy subjects for functional connectivity analysis.

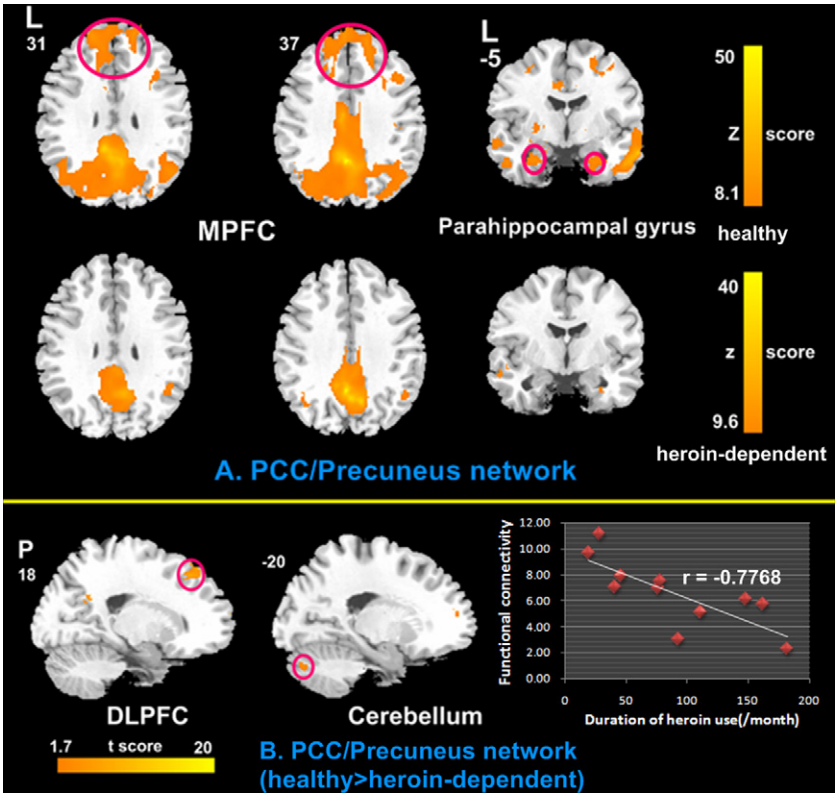

Fig. 2. (A) PCC/Precuneus network (upper: healthy subjects; lower: heroin-dependent individuals). (B) Two-sample *t*-test result of PCC/Precuneus network and correlation analysis. Compared with healthy subjects, heroin-dependent individuals showed significantly reduced functional connectivity between PCC/Precuneus and right cerebellum and left DLPFC. The functional connectivity between PCC/Precuneus and right cerebellum was significantly negative correlated with duration of heroin use (*r*: correlation coefficient).

were constructed by computing F-contrasts, which compared the effect of signal fluctuations in the range of 0.01–0.1 Hz. Statistical parametrical maps were created under the threshold $p < 0.005$ (corrected for multiple comparisons) at the first level. The final overlapping mask was created by multiplying the binary values of the individual mask in each group. Finally, the conjunction analysis of two group masks was applied to detect inter-group similarities of spatial patterns, which was adopted as the region of interest (ROI) for the functional connectivity analysis [15].

We applied the ROIs derived from DCT conjunction analysis for resting-state functional connectivity analysis. For each subject, correlation analysis was conducted between the ROI and the rest of the whole brain in a voxel-wise manner. The resulting correlations were transformed to approximate Gaussian distribution using Fisher's *z* transformation [23] and then analyzed with a random effect one-sample *t*-test to identify voxels showing a significantly positive correlation to the seed time series within heroin-dependent individuals and healthy subjects. For between-group comparison, two-sample *t*-test was used to compare *z* value maps between heroin-dependent individuals and healthy subjects ($p < 0.05$, small volume corrected). To identify the association between functional connectivity of ROIs and heroin dependence, the average *z* scores of brain regions which showed reduced functional connectivity with ROIs during resting-state in heroin-dependent individuals were extracted and correlated with duration of heroin use, controlling for age and education as covariates.

Our results demonstrated that spontaneous fluctuations in the resting-state were detected in similar widespread areas throughout the brain in heroin-dependent individuals and healthy subjects. Spontaneous signal changes were present in posterior cingulate cortex (PCC)/Precuneus, ACC, inferior parietal lobe, supplementary motor area (SMA), middle temporal lobe, and occipital lobe in heroin-dependent individuals and healthy subjects (Fig. 1).

Previous studies reported that PCC is the key nodes of default mode network (DMN) [5,10] and rACC plays an important role in inhibitory control [13], so we chose these two regions from the overlapping regions in DCT conjunction analysis as our ROIs for subsequent functional connectivity analysis.

In healthy subjects, PCC/Precuneus showed significant functional connectivity with the following regions: a large cluster of MPFC, including ACC and OFC; DLPFC; parahippocampal gyrus; angular gyrus and middle temporal lobe all bilaterally (family-wise error (FWE) correction at $p < 0.05$). In heroin-dependent individuals, these regions were only located in bilateral middle temporal lobe and angular gyrus and right DLPFC (FWE correction at $p < 0.05$). Compared with healthy subjects, heroin-dependent individuals showed significantly reduced functional connectivity between PCC/Precuneus and right cerebellum and between PCC/Precuneus and left DLPFC ($p < 0.05$, corrected). Functional connectivity between PCC/Precuneus and right cerebellum was significantly negative correlated ($r = -0.7768$, $p = 0.0049$) with duration of heroin use in heroin-dependent individuals, including age and education as covariates (Fig. 2). No regions showed enhanced functional connectivity with PCC/Precuneus in heroin-dependent individuals.

In healthy subjects, the regions showing significant functional connectivity with rACC included bilateral hippocampus; middle temporal lobe; OFC and left PCC (FWE correction at $p < 0.05$). In heroin-dependent individuals, rACC showed functional connectivity with bilateral thalamus and OFC; left middle temporal lobe (FWE correction at $p < 0.05$). Heroin-dependent individuals showed significantly reduced functional connectivity between

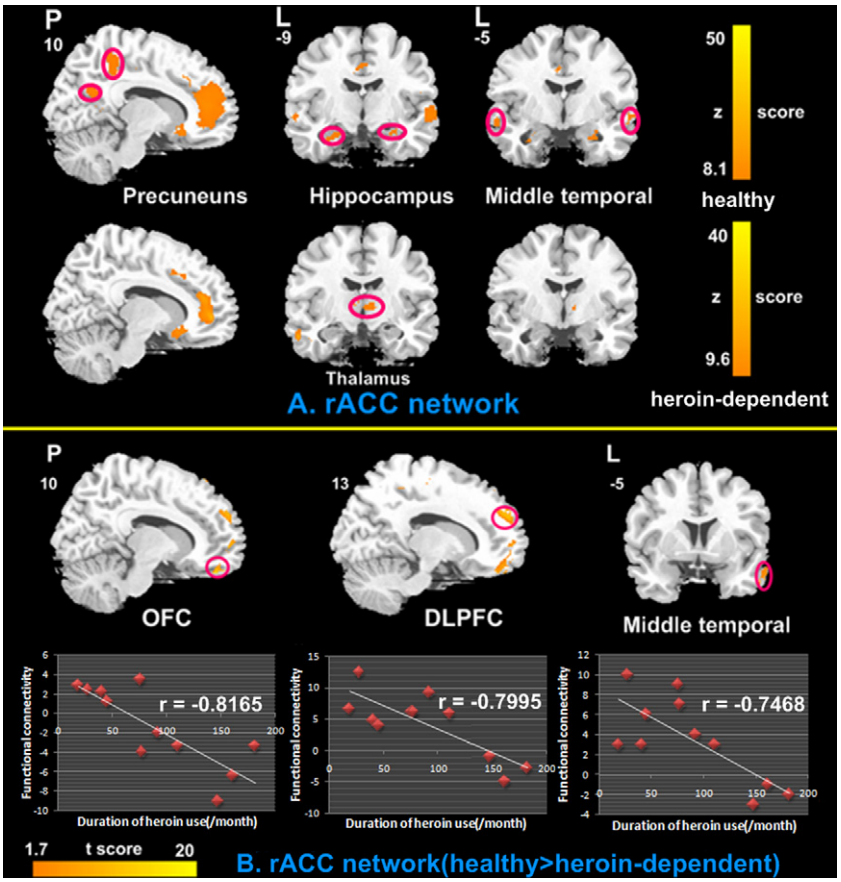

Fig. 3. (A) rACC network (upper: healthy subjects; lower: heroin-dependent individuals). (B) Two-sample *t*-test result of rACC network and correlation analysis results. Heroin-dependent individuals showed significantly reduced functional connectivity between rACC with left OFC, DLPFC and right middle temporal lobe and these alterations showed negatively correlation with duration of heroin use (*r*: correlation coefficient).

rACC with several regions consisting of left OFC, DLPFC and right middle temporal lobe ($p < 0.05$, corrected). Furthermore, these resting-state functional connectivity alterations were negatively correlated with duration of heroin use (OFC: $r = -0.8165$, $p = 0.0022$; DLPFC: $r = -0.7995$, $p = 0.0031$; middle temporal lobe: $r = -0.7468$, $p = 0.0083$) in heroin-dependent individuals, including age and education as covariates (Fig. 3). No regions showed enhanced functional connectivity with rACC in heroin-dependent individuals.

In the present study, we combined spatial and temporal information to explore resting-state networks changes in abstinent heroin-dependent individuals. We first applied DCT to explore the spatial distribution of low frequency BOLD oscillations in resting-state in heroin-dependent individuals and healthy subjects. Consistent with previous studies [4,15], we found a prominent presence of fluctuations in several brain regions, including PCC/Precuneus and rACC, in healthy subjects (Fig. 1). The heroin-dependent individuals DCT map was similar to healthy subjects. However, previous heroin studies had found structural changes and functional impairments in heroin-dependent individuals [6,13,14,16,17,25,26], we continued to study the temporal characteristics of brain regions with similar spatial patterns derived from DCT conjunction analysis.

Fransson and Marrelec [5] found that the PCC/Precuneus was the only region that directly interacts with virtually all other regions in the DMN, using partial correlation analysis. They suggested that the PCC/Precuneus play a pivotal role in the DMN. In the present study, we chose the PCC/Precuneus as first ROI to detect PCC/Precuneus ntework (i.e. DMN) changes in heroin-dependent individuals. Compared with healthy subjects, heroin-dependent individuals showed significantly reduced functional connectivity between PCC/Precuneus and right cerebellum ($p < 0.05$, corrected). In addition, the functional connectivity between PCC/Precuneus and right cerebellum during resting-state was negatively correlated with duration of heroin use in heroin-dependent individuals (Fig. 2). Our results provided plausible evidences for cerebellum's potential role in heroin addiction [22]. One prevailing view is that DMN involves retrieval and manipulation of past events to make decisions [10]. We suggested the decreased functional connectivity between PCC/Precuneus and right cerebellum in DMN weakens the decision-making function in heroin-dependent patients.

Recent neuroimaging studies have disclosed deactivation of the rACC in a GO/NOGO task in heroin-dependent individuals [1,6], indicating rACC's essential role in response inhibition and inhibitory control [13]. In addition, emotional stress is revealed to contribute to drug use and relapse [19,21]. The exposure to stress was found to aggravate drug craving and relapse [2,20], which centrally involves rACC [13]. Therefore, the overlapping rACC in DCT conjunction analysis was identified as the second ROI. Heroin-dependent individuals showed significantly reduced functional connectivity between rACC and other regions, including left OFC, DLPFC and right middle temporal lobe ($p < 0.05$, corrected). Negative correlation was observed between these functional connectivity alterations and duration of heroin use in heroin-dependent individuals (Fig. 3). These results indicated that the information communication between rACC and these regions (OFC, DLPFC and middle temporal lobe) decreased along with chronic heroin use. Previous neuroimaging studies concerning with the disruption of OFC and DLPFC in drug users have provided evidence for OFC and DLPFC's role in decision-making and motivation-relevant processes [8,9,24]. Our results were likely to be

associated with the functional impairments in response inhibition and decision-making exhibited by heroin-dependent individuals [6,9,25].

Volkow et al. [22] have proposed the four-circuit model for addiction: (1) reward, located in NAc and ventral pallidum; (2) motivation/drive, located in OFC and subcallosal cortex; (3) memory and learning, located in amygdala and hippocampus; and (4) control, located in the prefrontal cortex and ACC. In this model, drug addiction is 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 [22]. These functional changes result in an enhanced and permanent saliency value for the drug, and in loss of inhibitory control, finally leading to emergence of compulsive drug administration and relapse [22]. The control circuit modulates the "output" of non-addicted brain by communicating with the reward circuit and motivation/drive circuit. In addicted brain, the communication between control circuit and motivation/drive circuit vanished and this leads to drug craving and relapse. We also would like to reason that our results provide insights into heroin addiction by showing the rACC-OFC (control circuit and motivation/drive circuit) functional connectivity decreased along with chronic heroin use in heroin-dependent individuals. Our findings provided useful information for the therapeutic interventions and suggested that more attention should be paid to the pattern of information transmission and processing between control circuit and motivation/drive circuit in heroin-dependent individuals.

Several limitations should be considered when interpreting the results of present study. First, the sample is small (11 male heroin-dependent individuals). The results should be checked in a larger sample and gender-matched group. Second, our subjects had received Methadone maintenance treatment (MMT) for their chronic heroin use for about 5 months. We cannot rule out the MMT effects on brain structural and functional. Future studies are recommended to assess such effects by comparing short-term MMT patients with long-term MMT patients. We failed to test whether these resting-state abnormalities in heroin-dependent individuals are the consequence of chronic heroin use in the present study.

In conclusion, we observed that the default mode network (DMN) and rostral anterior cingulate cortex (rACC) network were changed in heroin-dependent individuals and these changes negatively correlated with duration of heroin use. These findings may explain the behavioral and neuropsychological deficits in heroin-dependent individuals and will shed light on the mechanism underlying heroin addiction.

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