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Neuroscience Letters 482 (2010) 101–105

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Gray matter deficits and resting-state abnormalities in abstinent heroin-dependent individuals

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ARTICLE INFO

Article history:
Received 27 May 2010
Received in revised form 1 July 2010
Accepted 1 July 2010

Keywords:
Heroin
Voxel-based morphometry
Resting-state

ABSTRACT

Previous neuroimaging studies have demonstrated both structural and functional damages in heroin-dependent individuals. However, few studies investigated gray matter deficits and abnormal resting-state networks together in heroin-dependent individuals. In the present study, voxel-based morphometry (VBM) was used to identify brain regions with gray matter density reduction. Resting-state fMRI connectivity analysis was employed to assess potential functional abnormalities during resting-state. All clinical significances were investigated by examining their association with duration of heroin use. Compared with healthy subjects, heroin-dependent individuals showed significant reduction in gray matter density in the right dorsolateral prefrontal cortex (DLPFC) and a decrease in resting-state functional connectivity between the right DLPFC and left inferior parietal lobe (IPL). The gray matter density of the right DLPFC and its resting-state functional connectivity with the left IPL both showed significantly negative correlation with duration of heroin use, which were likely to be related to the functional impairments in decision-making and cognitive control exhibited by heroin-dependent individuals. Our findings demonstrated that long heroin dependence impairs the right DLPFC in heroin-dependent individuals, including structural deficits and resting-state functional impairments.

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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 [11]. Emerging morphometry studies have reported structural deficits in heroin-dependent individuals, such as 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 as compared with healthy subjects [18,19,28]. Recently, Yuan et al. [28] showed that gray matter density of the prefrontal, temporal and cingulate cortices in heroin-dependent individuals was negatively correlated with the duration of heroin use. However, the authors failed to investigate the resting-state abnormalities of these abnormal structural brain regions in heroin-dependent individuals.

In addition, functional impairments in heroin-dependent individuals have also been verified by employing task-related fMRI methods [9,15,25]. Numerous neuroimaging studies have revealed impaired response inhibition function and decision-making function in heroin-dependent subjects by presenting hypoactivation of the prefrontal and rostral anterior cingulate cortex (ACC) in certain tasks [9,15,25]. Although fMRI task-related studies can investigate specific functional disturbances in heroin-dependent individuals, assessment of resting-state functional networks may have different and potentially broader significance. Resting-state functional connectivity analysis has been utilized to investigate the integration level of neural systems when no explicit task was engaged and the results demonstrated correlated spontaneous activity occurring within spatially distinct, functionally related groups of brain regions during task-free conditions [7,8,12]. Recently, assessments of resting-state networks have also been conducted in heroin addiction [16,20,26]. Ma et al. [20] adopted the seed-based regions of interest (ROIs) correlation analysis method and observed alteration in resting-state brain connectivity in heroin-dependent individuals, i.e. increased functional connectivity between the nucleus accumbens (NAc) and ACC, the NAc and orbitofrontal cortex

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doi:10.1016/j.neulet.2010.07.005

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(OFC), and the amygdala and OFC; reduced functional connectivity between the prefrontal cortex and OFC and the prefrontal cortex and ACC. Our group employed the graph theory analysis (GTA) method and reported the correlations between the abnormal topological properties in the brain of heroin-dependent individuals and heroin dependence [16,27]. More recently, we observed that the default mode network (DMN) and rostral ACC network of heroin-dependent individuals were altered in comparison with healthy subjects, and these changes were negatively correlated with the duration of heroin use [26]. All of these resting-state functional abnormalities in heroin-dependent individuals provided evidence for abnormal functional organization in heroin-dependent individuals and enhanced our understanding of heroin addiction [16,20,26]. Numerous heroin studies reported structural deficits and functional impairments in heroin-dependent individuals [16,20,26–28]. However, few studies connected the gray matter density reduction with resting-state functional connectivity alterations in heroin-dependent individuals. The purposes of the present study were to (1) identify brain regions with gray matter density reduction in heroin-dependent individuals employing voxel-based morphometry; (2) investigate the clinical significance of gray matter density reduction and functional connectivity of these anatomic deficits by focusing on their association with duration of heroin use.

The experimental protocol was approved by the Institutional Review Board of The Fourth Military University, China. Due to data limitation (few female patients in the treatment center), eleven abstinent heroin-dependent males (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. To avoid the confounding from comorbidity of drug use, we carefully selected participants who were not dependent on other psychoactive drugs and reported no history of use of these drugs, except heroin and nicotine. These subjects occasionally drank alcohol during social activities. Any psychoactive substances, except for cigarettes, were strictly forbidden during treatment in the drug rehabilitation center. Exclusion criteria included psychiatric, neurological, and medical disorders requiring immediate treatment; additional current substance abuse/dependence diagnosis; and contraindications to MRI 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 was 4.9 ± 0.8 months (range 3–6 months) and a negative test for the presence of morphine in urinalysis (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. The scanning took place at least 5–8 h after daily methadone use; a time point when the methadone plasma level was stable with daily dosing [14].

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 who never used any psychoactive substances except drinking a small amount of alcohol during social occasions. None of the subjects was taking prescription drugs that affected the central nervous system within 1 week of scanning 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 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.

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

	Healthy subjects ($n = 13$)	Heroin-dependent individuals ($n = 11$)
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
Nicotine use (no. of cigarette/day)	N/A	15.4 ± 10.7

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 sequence (3D-FSGPR) (matrix 256 × 256; FOV = 256 mm × 256 mm; spatial resolution = 1 mm × 1 mm × 1 mm; TE = 7.8 ms; TR = 3.0 ms). A gradient echo T2*-weighted sequence with an in-plane resolution of 3.75 mm × 3.75 mm was acquired (TE = 30 ms, TR = 2 s, matrix = 64 × 64, FOV = 240 mm, and flip angle = 90°). About 150 echo-planar volumes were acquired during the resting scan, while functional imaging scanning lasted 5 min. Subjects were instructed to keep their eyes closed, not to think about anything, and to stay awake during all scans. After scanning, all subjects reported that they all stayed awake during all scans.

Classical VBM was conducted using Statistical Parametric Mapping-5 (SPM5) (http://www.fil.ion.ucl.ac.uk/spm). Gray matter was automatically segmented from raw MRI by employing the unified segmentation-normalization approach in SPM5 [1]. Gray matter partitions were spatially normalized to the gray matter template of SPM5 and resampled to 1 mm^3. The deformation parameters obtained from the normalization process were applied to each subject's original raw image (native space) in order to create optimally normalized whole brain images, which were recursively segmented for brain tissue extraction. Finally, the segmented images were modulated with the Jacobian determinants derived from spatial normalization [2]. The optimally processed images were smoothed with an isotropic Gaussian kernel (full-width half maximum (FWHM) = 8 mm).

Voxel-by-voxel-based comparisons of gray matter density were performed between groups using two-sample *t*-tests by controlling for the possible effects of age and years of education ($p < 0.05$, corrected for multiple comparisons). To identify the association between structural abnormalities and heroin dependence, the average gray matter density of reduced brain regions of heroin-dependent individuals was extracted and correlated with the duration of heroin use controlling for age, education, and nicotine usage.

To assess resting-state properties in those structurally impaired brain regions, we employed the functional connectivity method. We chose the right dorsolateral prefrontal cortex (DLPFC) as the "seeding" region for the functional connectivity analysis, because (1) VBM regression analysis showed that the gray matter density in the right DLPFC had significant negative correlation with the duration of heroin use; (2) a previous study revealed functional impairment of the DLPFC in heroin-dependent individuals [24]. The preprocessing steps were performed according to a previous publication in SPM5 [17], i.e. realignment, normalization, bandpass

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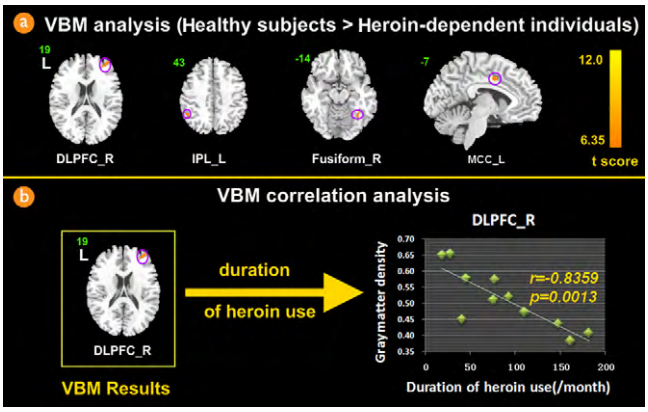

Fig. 1. (a) VBM analysis (healthy subjects > heroin-dependent individuals). (b) VBM correlation analysis (*r*: correlation coefficient, *p*: *p* value). DLPFC: dorsolateral prefrontal cortex; IPL: inferior parietal lobe; MCC: middle cingulate cortex; L: left; R: right.

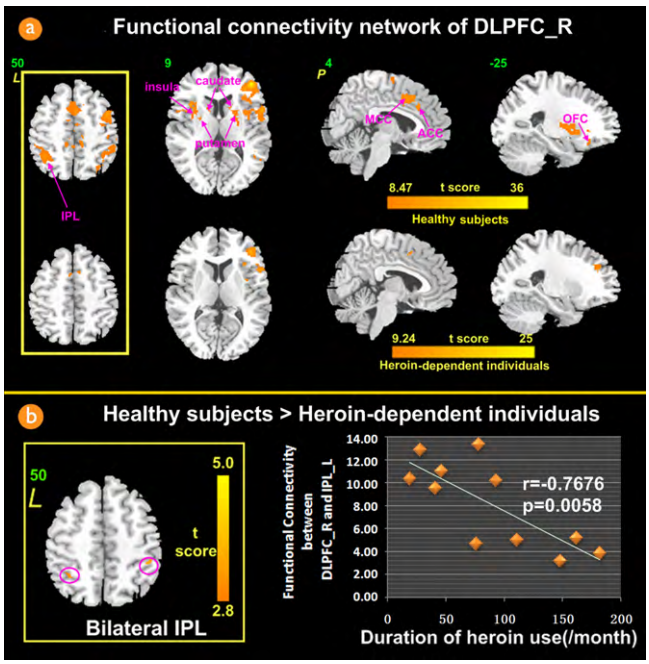

Fig. 2. (a) Functional connectivity networks of the right DLPFC ($p < 0.05$, FWE corrected). (b) Different connectivities between healthy subjects and heroin-dependent individuals ($p < 0.05$, corrected) and correlation analysis (*r*: correlation coefficient, *p*: *p* value). DLPFC: dorsolateral prefrontal cortex; IPL: inferior parietal lobe; MCC: middle cingulate cortex; ACC: anterior cingulate cortex; OFC: orbital frontal cortex; L: left; R: right; P: posterior.

filter (0.01–0.08 Hz) [17,23] and smoothing (FWHM = 8 mm). Functional connectivity was examined using a method based on a seed voxel correlation approach [17]. For each subject, the correlation analysis was conducted between the seed reference and the rest of the whole brain in a voxel-wise manner by regressing out the effects of head motion parameters. 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 (family-wise error (FWE) correction at $p < 0.05$). For between-group comparison, two-sample *t*-tests were used to compare *z* value maps between heroin dependents and healthy comparison subjects ($p < 0.05$, corrected). To identify the association between functional connectivity of the right DLPFC and heroin dependence, the average *z* scores of brain regions which showed reduced functional connectivity with the right DLPFC during resting-state in heroin-dependent individuals were extracted and correlated with duration of heroin use including age, education and nicotine usage as covariates.

Relative to healthy subjects, heroin-dependent individuals showed a significant reduction in gray matter density in the right DLPFC, left IPL, right fusiform gyrus and left middle cingulate cortex (MCC) (Fig. 1a). No significant increases in gray matter density were found. Gray matter density of the right DLPFC in heroin-dependent individuals was found to be negatively correlated ($r = -0.8359$, $p = 0.0013$) with the duration of heroin use (Fig. 1b).

In healthy subjects, several brain regions were found to be positively correlated with the right DLPFC: insula, putamen, caudate, MCC, IPL, ACC, OFC (all bilaterally), right thalamus and right fusifrom gyrus ($p < 0.05$, FWE corrected). However, in heroin-dependent individuals few regions, including the insula, MCC, fusiform gyrus, IPL (all in the right cerebrum), showed positive correlation with the right DLPFC ($p < 0.05$, FWE corrected). Compared with healthy subjects, heroin-dependent individuals showed significantly reduced functional connectivity between the right DLPFC and bilateral IPL ($p < 0.05$, corrected) (Fig. 2a). A significantly negative correlation ($r = -0.7676$, $p = 0.0058$) was observed between the duration of heroin use and functional connectivity between the right DLPFC and left IPL in heroin-dependent individuals (Fig. 2b).

Although several heroin studies revealed structural deficits and resting-state functional network abnormalities in heroin-dependent individuals [20,26–28], few studies have made a connection between the structural (gray matter density) and functional (resting-state functional connectivity) brain alterations in heroin-dependent individuals. In the present study, VBM was used to identify brain regions with gray matter density reduction; meanwhile, a resting-state fMRI connectivity analysis was employed to assess potential functional abnormalities of these brain regions during resting-state in heroin-dependent individuals.

We found that heroin-dependent individuals showed significantly decreased gray matter density in the right DLPFC, left IPL, right fusiform gyrus and left MCC (Fig. 1a), which was consistent with previous studies [18,28]. Furthermore, the gray matter density of the right DLPFC was negatively correlated with the duration of heroin use (Fig. 1b). The correlation results demonstrated that heroin use has a cumulative effect; the longer the heroin use, the lower the level of gray matter density in some heroin addiction-related brain regions. Numerous studies revealed that drug-related cues elicited significant activation of the DLPFC in active drug users [4,6,10]. Moreover, DLPFC neurons encode reward expectancy during a delay, and delay activity of DLPFC neurons has been shown to predict subsequent behavioral responses in rewarded tasks [22]. Some animal studies demonstrated that lesions in the rat prelimbic cortex (the functional homologue of the human DLPFC) impaired the acquisition and modification of behavior guided by contingencies between responses and outcomes, indicating that these regions may be crucial for the cognitive control of goal-directed behavior [3]. Previous studies also suggested that the DLPFC is centrally involved in decision-making tasks [13], which require the integration of cognitive and motivationally relevant information [24]. Our results of reduced gray matter intensity in the DLPFC may be, in part, associated with decision-making and goal-directed behavior dysfunctions in heroin dependence [18,20,25]. Several studies reported that the IPL integrated information from different sensory modalities and played an important role in a variety of higher cognitive functions [5]. The bilateral IPL is also frequently activated during working memory paradigms in both humans and animals [12]. In addition, Park et al. [21] reported that significant activation was observed in the bilateral IPL and right fusiform gyrus among subjects with alcohol use disorders in response to alcohol cues.

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The gray matter density reduction of the IPL in the present study may provide some implications for functional deficits such as working memory and higher cognition in heroin-dependent individuals [9,16,25]. Recently, heroin-related cues were also reported to elicit activity in the bilateral fusiform gyrus in heroin-dependent individuals [25]. Our results provided evidence for the possible role of the fusiform gyrus in heroin addiction, which may be related with functional abnormalities in recognition.

As gray matter density of the right DLPFC was reduced in heroin-dependent subjects and it showed a negative correlation with the duration of heroin use, we chose this region as our ROI to investigate resting-state functional connectivity changes in heroin-dependent individuals. Compared with healthy subjects, heroin-dependent individuals showed significantly decreased functional connectivity between the right DLPFC and bilateral IPL (Fig. 2). More importantly, a significantly negative correlation was observed between the duration of heroin use and functional connectivity between the right DLPFC and left IPL in heroin-dependent individuals (Fig. 2). These results demonstrated that as the heroin use persisted, the information communication between the right DLPFC and left IPL decreased, which may provide some implications for the functional impairments in decision-making and cognitive control exhibited by heroin-dependent individuals [9,25]. In our results, gray matter deficits of the right DLPFC and corresponding resting-state functional connectivity abnormalities in abstinent heroin-dependent individuals suggested that long heroin dependence influenced the right DLPFC. It is possible to speculate, therefore, that the gray matter density reductions of the right DLPFC led to a systems-level alteration in functional connectivity [9,25]. It is important to note, however, that the causal relationship between gray matter density and functional connectivity is unknown. Evidently, more work is needed to understand this fascinating phenomenon. The method in our study connects the brain structural (gray matter density) and functional (resting-state functional connectivity) alterations in heroin-dependent individuals, will enhance our understanding of opiate addiction.

Several limitations should be considered when interpreting the results of this study. First, the sample size is small (11 heroin-dependent individuals). Better results will be obtained with a larger sample and a gender-matched group. Second, our subjects received methadone maintenance treatment (MMT) for their chronic heroin use for about 5 months. We cannot rule out the MMT effects on the structural and functional aspects of the brain. Future studies are recommended to assess such effects by comparing short-term MMT patients with long-term MMT patients. Third, since heroin-dependent individuals in our study have used nicotine, our results might be confounded. In view of this, we employed the covariate procedure in the partial analysis.

In conclusion, our results revealed gray matter deficits of the right DLPFC and its resting-state functional connectivity abnormalities in abstinent heroin-dependent individuals. More importantly, all of these structural and functional impairments were significantly negatively correlated with the duration of heroin use. Our results demonstrated that long-term heroin dependence influenced the right DLPFC, including structural deficits and functional impairments during the resting-state. Our findings hope to shed light on the mechanisms underlying opiate addiction.

Acknowledgments

This paper is supported by Changjiang Scholars and Innovative Research Team in University (PCSIRT) under Grant No. IRT0645, the Chair Professors of Cheung Kong Scholars Program of Ministry of Education of China, CAS Hundred Talents Program, the National Natural Science Foundation of China under Grant Nos. 30970774, 60901064, 30873462, 30870685, the Knowledge Innovation Program of the Chinese Academy of Sciences under Grant No. KGCX2-YW-129, the Project for the National Key Basic Research and Development Program (973) under Grant No. 2006CB705700, the 863 program under Grant No. 2008AA01Z411, and the Fundamental Research Funds for the Central Universities.

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