Brain function of heroin addicts after withdrawal

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Abstract: Objective To explore what brain regions are modulated by heroin addiction and withdrawal. **Methods** We used functional magnetic resonance imaging to investigate the brain function in 15 heroin-dependent patients 3 days (acute) and 1 month (protracted) after heroin abstinence. Sixteen normal controls were included. **Results** The blood oxygen level-dependent signal in the orbitofrontal cortex of the brain of heroin-dependent patients was significantly elevated 3 days after the withdrawal. Hyperfunction of the orbitofrontal cortex declined 1 month after the withdrawal. **Conclusion** Heroin-dependent subjects at both 3 days and 1 month abstinence have persistent abnormalities in the brain function. Although some tangible beneficial effects are noted following 1 month of detoxification, possible permanent damage to the brain caused by heroin use is suggested.

Key words: heroin; abstinence; functional magnetic resonance imaging; blood oxygen level dependent

海洛因成瘾者停止吸毒后的脑功能变化

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[**摘要**] **目的:**探讨海洛因成瘾者在戒断期的脑功能的变化。**方法:**用功能磁共振检测15位海洛因成瘾者停止吸毒3 d和1个月的静息状态下脑功能情况,并与16位正常对照者进行比较。**结果:**海洛因成瘾者在停止吸毒3 d后功能磁共振成像显示其额叶出现血氧水平依赖(blood oxygen level dependent, BOLD)信号增加;而停止吸毒1个月后,BOLD信号的增加恢复正常。**结论:** 海洛因成瘾者戒断后仍有脑功能的异常,其中部分异常可以随着戒断时间的延长而恢复。

[**关键词**] 海洛因; 戒断; 功能性磁共振成像; 血氧水平依赖

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Drug addiction is characterized by drug craving and compulsive withdrawal/relapse. The withdrawal/relapse cycle can last a lifetime and has posed a great challenge for clinical treatment of drug-dependent patients. The nucleus accumbens, the ventral tegmental area, and some limbic brain regions are

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traditionally considered to be the neural regions targeted by drug addiction[1-2]. Nevertheless, it has been noted that several major features of addiction such as relapse to drug use following prolonged abstinence and the transition from controlled drug intake to excessive and compulsive drug use can not simply explained by the acute rewarding effects of drugs. Thus, a new theory about drug addiction has begun to emerge and stipulates that changes in multiple brain circuits, including those are involved in reward/saliency, motivation/drive, inhibitory control/disinhibition, and memory/conditioning are responsible for the development and maintenance of addicted state[3].

Brain imaging techniques have been used to identify specific brain regions and neural targets associated with drug addiction[3-4]. Studies using position emission tomography (PET) and functional magnetic resonance imaging (fMRI) have shown that the frontal, temporal, and cingulate cortices, and several other brain structures are engaged in drug addiction[3]. The frontal cortex appears to be most frequently involved. Acute drug use increases the blood oxygen level-dependent (BOLD) signal and regional cerebral blood flow (rCBF) in the frontal lobe[5-6]. The rCBF in the frontal lobe decreases during withdrawal[7] and increases during craving[8]. Structural MRI studies have also shown abnormal changes in tissue composition and in the volume of certain brain regions of drug abusers[4]. Decreased white matter volume (WMV) is found in the frontal cortex of polysubstance abusers[9], while decreased gray matter volume (GMV) is noted in the frontal and temporal cortices, thalamus and cingulate cortices, and cerebellum of cocaine or methamphetamine abusers[10-11]. On the other hand, enlarged basal ganglia has also been found in cocaine- and methamphetamine-dependent subjects[12-13]. Moreover, a recent study has reported a decreased gray matter density (GMD) in the frontal and temporal cortices of heroin-dependent patients[14]. It is clear that many factors could affect these imaging-based drug addiction studies. These include type of addictive drugs, duration and dosage of drug intake, and age and education of subjects. Very few of these studies have looked into the changes of functional and structural abnormalities of the brain in the context of drug withdrawal, particularly in heroin addicts, despite the fact that drug withdrawal is an important part of drug craving, relapse and treatment. Early fMRI reports focused on stimulus-induced BOLD signal increments. Recent development in fMRI has made it possible to analyze BOLD signal in the "resting" state[15-16]. Thus, in this study, we attempted to determine any long-lasting effects of heroin dependence on brain function in rest using fMRI techniques. More importantly, we used these imaging techniques to determine how these effects evolved during drug abstinence, i.e. 3 days acute heroin withdrawal and 1 month protracted heroin withdrawal.

1 SUBJECTS AND METHODS

1.1 Subjects

Fifteen heroin-dependent patients were recruited through inpatient facilities at the Drug Treatment and Rehabilitation Center of Changsha City, Hunan Province, P. R. China. Sixteen healthy subjects with no contraindications for MRI scans were recruited from the community and matched for age and education levels to the heroin-dependent subjects. Every subjects had been interviewed by two senior psychiatrists. A detailed medical history, brief neurological examination and a number of clinical laboratory tests (blood count, urinary analysis, comprehensive metabolic panel, urine drug screen) had been done to ensure that they had no major neurological/psychiatric disorders or other drug abuse (except smoking). All of the patients were not given any drug treatment for heroin addiction in Drug Treatment and Rehabilitation Center, all the health controls were required to have no medications for at least 2 weeks prior to screening.

All participants were Han Chinese men. All patients met the following inclusion criteria: 1) diagnostic and statistical manual of mental disorders, fourth edition (DSM-IV) criteria for substance dependence and urine sample positive for heroin when entering the drug treatment center; 2) aged between 18 and 48 years; 3) no neurological or significant

physical disorders; 4) absence of abuse of other substances except nicotine; 5) right-handedness; and 6) not under drug treatment for heroin addiction. The control individuals also met criteria 2), 3), and 4). All participants were given written informed consent, and the study protocol was approved by the Ethics Committee of Central South University, Hunan Province, P. R. China.

The mean age of the heroin patients was (30.31 ± 6.65) years, the mean education was (9.64 ± 2.19) years. The mean age of the control subjects was (29.42 ± 5.33) years, the mean education was (10.11 ± 2.41) years. There was no statistical difference in the age or education level between patients and the healthy controls ($P > 0.05$). The patients had used heroin for an average of (4.05 ± 2.21) years. They reported using heroin a mean of (1.16 ± 0.72) gram per day. All the participants including heroin-addicts and controls were smoking, but the heroin-addicts [(31.14 ± 6.76) cigarettes per day] used more cigarettes than the controls [(17.48 ± 6.21) cigarettes per day].

1.2 Imaging acquisition

All subjects underwent resting-state scan in which they were given no specific instructions except to keep their eyes closed and hold still[16]. Images were acquired on all subjects twice: once on 3 days after withdrawal and once at one month after withdrawal using a GE Signa 1.5 T scanner (General Electric Co., Fairfield, Connecticut, USA) equipped with high-speed gradients. The subject's head was positioned within a prototype quadrature birdcage head coil that was specifically developed for functional imaging of the brain. Foam padding was used to restrain head movement. To eliminate the individual difference, heroin addicts were scanned twice.

Subjects were scanned in a conscious natural resting state[17-18]. Data were acquired in a GE Signa System operating at 1.5 T with a gradient echo EPI sequence (TR = 2 000 ms, TE = 40 ms, FOV = 24 cm, matrix = 64 × 64 × 20, slice thickness = 5 mm, and gap = 1 mm).

1.3 Statistical analysis

Data were analyzed using the SPM2 software package (http://www.fil.ion.ucl.ac.uk/spm). Spatial transformation (realignment and spatial normalization) was performed. Then, the data were smoothed spatially with a Gaussian filter [8-mm full-width half-maximum (FWHM) kernel].

After preprocessing, the model was specified and the parameters were estimated. The autoregressive (AR) model was utilized to correct for any autocorrelation. The blood flow of each subject from both the healthy and patient groups was analyzed using a one-sample t test ($P < 0.005$ uncorrected). Random effect analysis was subsequently performed on all the subject-specific results. Differences among the patients after 3 days withdrawal, the patients after one-month withdrawal and the healthy subjects were tested by ANOVA analysis ($P < 0.005$ uncorrected)[19-20].

2 RESULTS

2.1 Three-day abstinence vs. healthy subjects

Compared with the BOLD signals of the healthy subjects, the BOLD signal in bilateral orbitofrontal cortex (Brodmann areas 11) was significantly higher in the heroin abusers after a 3-day abstinence interval ($P < 0.005$ uncorrected, Tab. 1); however, the BOLD signals in the cerebellar tonsil of the heroin abusers after a 3-day abstinence interval were significantly lower ($P < 0.005$ uncorrected, Tab. 1).

2.2 One-month abstinence vs. healthy subjects

As same as the heroin abusers after a 3-day abstinence, the BOLD signals in the cerebellar tonsil of the heroin abusers after 1-month abstinence interval were significantly lower ($P < 0.005$ uncorrected). Remarkably, there was no brain region showing significant higher BOLD signal in patients after 1-month abstinence interval as compared with healthy subjects.

2.3 Three-day abstinence vs. 1-month abstinence

Comparisons of the BOLD signals from the heroin-dependent subjects on the third day and one month of withdrawal revealed that the subjects tested during 3-day abstinence had a significantly higher BOLD signal in the cerebellar tonsil and Brodmann areas 10 and 45 than those tested during 1-month abstinence ($P < 0.005$ uncorrected, Tab. 2).

Tab. 1 BOLD signal in brain regions of patients after 3-day withdrawal compared with the healthy subjects ($P < 0.005$ uncorrected)

Items	Cluster size	L/R	Description of extent of cluster	BA	P	MNI coordinates		
						X	Y	Z
Patients < control	53	R	Cerebellar tonsil		0.000	52	−56	−48
Patients > control	39	L	Orbitofrontal	11	0.001	−14	30	−22
	31	R	Orbitofrontal	11	0.002	20	−10	76
	14	R	Orbitofrontal	11	0.002	10	−10	76
	20	L	Orbitofrontal	11	0.002	−12	−12	76

Cluster size is in the unit of voxel; L/R: Left/right hemisphere; BA: Brodmann area; MNI: Montreal neurological institute.

Tab. 2 Higher BOLD signal in brain regions of patients after 3-day withdrawal vs. patients after 1-month withdrawal ($P < 0.005$ uncorrected)

Cluster Size	L/R	Description of extent of cluster	P	MNI coordinates		
				X	Y	Z
21	R	Brodmann areas 10	0.002	24	66	−8
7	R	Brodmann areas 45	0.002	56	38	4
13	L	Cerebellar tonsil	0.004	−54	−56	−46

Cluster size is in the unit of voxel; L/R: Left/right hemisphere; MNI: Montreal neurological institute.

3 DISCUSSION

In this study, we showed that the BOLD signal was significantly elevated in the orbitofrontal cortex (Brodmann areas 11) after 3-day withdrawal when compared with normal controls. After 1-month withdrawal, the BOLD signals in orbitofrontal cortex (Brodmann areas 11) of the heroin abusers did not differ from that of the healthy subjects. Furthermore, comparisons of the BOLD signals between heroin abusers at 3-days and 1-month withdrawal stages revealed that heroin abusers at one month of abstinence had significantly decreased BOLD signals in the orbitofrontal cortex. Our findings illustrate that, like other substance abusers, heroin-dependent subjects showed higher brain activity in the orbitofrontal cortex during early withdrawal, and that this abnormal brain activity can be changed after one month of heroin abstinence[21]. Because the brain BOLD signal serves as an indicator of brain activity, our studies also showed that chronic heroin abuse altered brain function, including changes in the orbitofrontal cortex, which can, to some extent, be reversible after 1-month abstinence. Similar findings have been reported in both humans and animals exposed to methamphetamine and opiate abuse[22-24].

The clinical significance of the changes of BOLD signals in the orbitofrontal cortex of heroin-dependent subjects after abstinence is still not completely clear. Craving may be associated with this, persistent drug craving and compulsive relapse are the key features of drug addiction. The orbitofrontal cortex may be involved in the persistent craving feature. This brain structure receives direct and indirect (via the thalamus) projections from the nucleus accumbens, the ventral tegmental area, and other limbic brain regions, such as the amygdala, the cingulate gyrus, and the hippocampus, which are known to be involved in drug reinforcement. In turn, the orbitofrontal cortex provides dense projections to the nucleus accumbens. Because of its reciprocal connections, the orbitofrontal cortex can integrate information from various limbic areas, and can also modulate the response of these limbic brain regions to drug intake[25]. A significant association between craving and rCBF in the orbitofrontal cortex has been reported in subjects with cocaine, heroin, and methylphenidate addiction[4]. The compulsive drug self-administration, which is one of the hallmarks of drug dependence, may be also associated with the orbitofrontal. Previous studies have revealed that the function of this brain region is involved in decision-making processes in reward-related behavior[21], assessing the future consequences of an individual's own actions (response selection), inhibiting inappropriate behavior, and the conscious experience of drug intoxication, drug incentive salience,

expectation[26]. Imaging studies also have found that compulsions and impulsivity, which are present in drug addiction, are associated with increased metabolic activity in the orbitofrontal cortex[25]. The data above indicate that dysfunction in the orbitofrontal cortex is a key neural mechanism underlying addiction[21,25]. Thus, the current findings further confirm an abnormal function of the orbitofrontal cortex in heroin abusers. The changes of BOLD signals after abstinence in heroin-dependent subjects ameliorated to some extent may be underlying the change of craving, the compulsive drug self-administration and anxiety in patients with substance abuse disorders[21]. Our studies demonstrated that both after 3 days and 1 month of withdrawal, heroin-dependent patients had significantly decreased BOLD signals in the cerebellum, when compared with healthy subjects. This finding is consistent with previous imaging studies in cocaine abusers, which reported cerebellar activation when cocaine abusers are exposed to cocaine cues or when they are administered methylphenidate[27]. The changes in cerebellar function may reflect conditioned responses and expectancy to addictive substances. Animal studies have also shown the involvement of the cerebellum in conditioned drug responses and expectancy[28].

There are several limitations to this study. First, the number of subjects who scaned twice in our study is small and all of them are male. They may not be representative of all the heroin abusers. Second, the fMRI has less sensitivity for detecting perfusion abnormalities in human brain than PET or SPECT, so the changes in some brain regions may be not able to be detected in our study. Third, while the groups were similar in most categories, smoking status was difference between heroin abusers and control subjects. The influence of nicotine is difficult to be separated. The last, in this type of clinical study there are inaccuracies regarding exact amount and histories of drug use by the substance abusers as well as denial of drug use by the comparison subjects. Although we performed a careful physical examination and obtained routine laboratory tests, we did not test for all potential confounding diseases (e.g., HIV in the comparison subjects).

In summary, our studies showed that the chronic heroin use can lead to changes in brain function and structure in heroin abusers. We also showed that some of these alterations were notably recovered during 1 month of detoxification. These findings support the notion that drug use can lead to permanent changes of the brain function and structure and underscore the measurable benefits of abstinence from heroin abuse.

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