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Gray matter density negatively correlates with duration of heroin use in young lifetime heroin-dependent individuals

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ABSTRACT

Numerous studies have documented cognitive impairments and hypoactivity in the prefrontal and anterior cingulate cortices in drug users. However, the relationships between opiate dependence and brain structure changes in heroin users are largely unknown. In the present study, we measured the density of gray matter (DGM) with voxel-based morphometry in 30 lifetime heroin-dependent individuals who had abstained from drug use for 5 months, and 34 healthy participants. The DGM of the prefrontal, temporal and cingulate cortices significantly decreased in heroin addicts relative to the healthy group. Critically, partial correlation analysis, which controlled for age, education and gender factors as well as nicotine use and heroin abstinence duration, showed that the duration of heroin use negatively correlated with the DGM in heroin-dependent individuals. These results provide compelling evidence for structural abnormality in heroin-dependent individuals and further suggest that duration of heroin use is a critical factor leading to brain damage.

1. Introduction

Previous studies have consistently reported cognitive impairments associated with heroin use. Specifically, heroin-dependent subjects show higher impulsiveness during problem solving (Lee & Pau, 2002; Lee et al., 2001) and increased commission errors when performing response suppression tasks (Swann, Bjork, Moeller, & Dougherty, 2002). Functional brain imaging studies revealed abnormalities of neural activity in heroin-dependent subjects including hypoactivity in the prefrontal and anterior cingulate cortices (Daglish et al., 2001; Rapeli et al., 2006). Reduced blood oxygenation level dependent (BOLD) responses in the prefrontal and the anterior cingulate regions were reported to be associated with weak impulse control in these subjects (Lee et al., 2005). Furthermore, Forman et al. (2004) reported that activation of the anterior cingulate cortex (ACC) in healthy individuals was associated with occurrence of false alarm errors and level of activation in this region predicted task performance; however, in opiate-dependent individuals, error detection activity in the anterior cingulate cortex significantly decreased, along with poorer task performance.

Although there have been many behavioral and functional imaging studies with heroin-dependent individuals, only a few studies on brain structural changes associated with heroin use have been reported. The results of these studies are largely inconsistent. While Pezawas et al. (1998) reported a significant ventricular and cortical volume loss of the brain in recent abstinent opioid-dependent patients, others failed to find such brain structure changes either in current and lifetime heroin-dependent subjects (Amass, Nardin, Mendelson, Teoh, & Woods, 1992) or in short-term and long-term abstained subjects (Rose et al., 1996). More recently, Lyoo et al. (2004, 2006) reported increased white matter intensities, mainly in frontal areas, and decreased gray matter density in both frontal and temporal regions in abstinent heroin-dependent individuals. Notably, this sample had high levels of comorbidity of alcohol, marijuana and cocaine. Subsequently, Reid et al. (2008) studied abstinent heroin-dependent subjects with no comorbid use of other psychoactive substances except nondependent use of alcohol. They reported reduction of thalamic gray matter volume but did not find any changes in cerebral cortex. They also found that the reduced thalamic gray matter volume was significantly influenced by alcohol use.

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The results of previous brain structural studies are far from consistent and this inconsistency is at least partially due to diversity of heroin dependency, comorbidity of other drug use, and abstinence condition in the samples across different studies. In the present study, we used voxel-based morphometry (VBM) (Ashburner & Friston, 2000) to examine structural changes in a relatively large sample of lifetime heroin-dependent individuals. We carefully selected recently abstinent lifetime heroin-dependent individuals who reported no history of dependence of other commonly abused drugs, such as cocaine, marijuana, and cannabis. Special care was taken to ensure that they were not current and lifetime users of alcohol, as this was present in almost all published studies with heroin-dependent subjects and alcohol use has been shown to be associated with changes in brain structures. Since negative correlations between age and the density of gray matter (DGM) were frequently reported (Steen, Gronemeyer, & Taylor, 1995; Wisco et al., 2008), we recruited young subjects with a relative narrow rang of age to minimize the age effect on brain structure. As abstinent condition could also contribute to brain structural measures, we recruited those who had abstained from heroin use for about 5 months. Based on previous behavioral and functional brain imaging studies, we predicted that the heroin-dependent subjects would show decreased DGM in the prefrontal and temporal cortices, and more importantly, the changes of DGM would correlate with duration of heroin use. The latter should be consistent with Ersche et al. (2006), showing that task-related activation of the left orbitofrontal cortex was associated with duration of intravenous heroin use.

2. Materials and methods

2.1. Participants

The study was approved by the Ethics Committee of The Institute of Psychology, Chinese Academy of Science. Thirty right-handed lifetime heroin-dependent individuals were recruited from Tianjin An'kang Hospital, a drug rehabilitation center, where they received treatment for their heroin use for about 5 months (no methadone replacement treatment was administered). 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. Individuals with a history of psychiatric, neurological, and medical disorders requiring immediate medical attention were excluded. The mean duration of heroin use was 4.29 years, and the age of first heroin use ranged from 15 to 25 years old with a mean of 20.43 years. Daily heroin consumption was estimated for each subject, which varied between 0.5 g and 1.2 g/day before they abstained. In addition, to avoid the confounding from comorbidity of drug use, we carefully selected participants from a much larger sample to ensure that they 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 their social activities (seven of them drank more than once a week and all less than three times a week). Any psychoactive substances except cigarette were strictly forbidden during treatment in the drug rehabilitation center.

Thirty four age-, education-, and gender-matched healthy subjects (all right-handed) were also recruited at the Tianjin An'kang hospital. These healthy subjects did not have any current or past DSM-IV diagnoses, as assessed by the SCID-IV; and never used any psychoactive substances except drinking a small amount of alcohol in their social occasions.

Information about the demographic and clinical information of the heroin-dependent individuals and the healthy subjects is presented in Table 1. There were no significant differences in age and education level between the heroin-dependent and healthy subjects ($p > 0.05$). Written informed consent was obtained from all participants.

2.2. MR image acquisition

Brain MR imaging was performed using a 3.0T Philips whole-body MRI system. A three-dimensional TFE pulse sequence was used to produce 156 1-mm-thick contiguous sagittal images [time to echo (TE) = 7 ms, repetition time (TR) = 15 ms, 256 × 129 matrix, field of view (FOV) = 24 cm, flip angle = 25°, 1 number of excitation].

2.3. Optimized VBM

Sagittal images were 3D-reconstructed and then transformed to axial images using the MRIcro software (http://www.sph.sc.edu/comd/rorden/mricro.html). The optimized VBM protocol (Good et al., 2001a) was applied to preprocess gray and white matter images by VBM2 toolbox (http://dbm.neuro.unijena.de/vbm/vbm2-for-spm2/). In brief, a customized template and *a priori* probability maps for gray and white matter were created by averaging and smoothing all the images of the 64 subjects. Using these customized templates, we spatially normalized and segmented all of the images, and then we applied these deformation parameters to the original images, which were segmented again. The resulting images were smoothed with a 12-mm full width at half maximum isotropic Gaussian kernel. Significant differences were estimated using random Gaussian field theory (Worsley et al., 1996).

The optimized VBM method is rater-independent because the predefined procedure is sequentially conducted. In addition, the rater was blind to the subjects' clinical information. Statistical parametric mapping (SPM2, Wellcome Department of Imaging Neuroscience, London, UK) was executed in MATLAB 7.1 (MathWorks, Natick, MA, USA).

2.4. Statistical analysis

Smoothed images were compared between groups using an analysis of covariance (ANCOVA) model to control for the possible effects of age, gender and education years. To define the regions with significant group differences, we set the probability level at < 0.001 and the extent threshold at 300 isotropic voxels of 1.0 mm^3. Statistical analysis of group differences in demographic variables was conducted with SPSS for Windows (12.0 version). Continuous data were evaluated using independent *t*-tests. Be-

Table 1
Demographic characteristics of the participants.

	Addiction group ($n = 30$)	Healthy group ($n = 34$)
Age (year)[a]	25.0 (2.4)	23.97 (2.69)
Sex (men/women)[a]	15/15	19/15
Education year[a]	9.03 (2.63)	10.24 (3.09)
Duration (year)	4.29 (1.92)	0
Abstinence (month)	4.93 (1.04)	0
Age of first use (year)	20.4 (2.8)	0
Nicotine use (no. cigarette/day)	23.7 (11.3)	NA
Alcohol (time/week)	1.07 (2.33)	NA

Note: Duration, years of heroin use.

[a] No significant difference between the groups in age ($t_{62} = 1.55$, $p = 0.126$), sex composition ($x^2 = 1.23$, $p = 0.541$), or education years ($t_{62} = 1.665$, $p = 0.101$).

tween-group comparisons involving categorical data (i.e., sex composition) were assessed using Fisher's exact test.

To further examine the relationship between the duration of heroin use and DGM, we first conducted correlation analyses to ensure there were no significant correlations between age and DGM in each group ($p > 0.5$, for both the groups). We then conducted a partial correlation analysis in the heroin-dependent individuals. In addition, the variables used in the partial analysis fit normal distribution were checked beforehand with Normal P–P plots in SPSS, and no outliers or missing data were found.

3. Results

The heroin users, compared with the healthy subjects, showed significantly decreased DGM in the prefrontal, anterior cingulate, and temporal regions ($p = 0.001$, extent threshold = 300 voxels) (Fig. 1A). Similar results were produced when age, gender and educational level were not included as covariates.

The prominent regions showing decreased DGM were in the prefrontal areas, including BA45, 46, 9, 11, 25. Decreases in DGM were also observed in the insular (BA13), ACC (BA32), and the temporal cortex (BA20) (Fig. 1B, C and Table 2).

A partial correlation analysis was also conducted with the age of first heroin use, duration of abstinence, nicotine and alcohol use included as controlling variables. We found that the DGM in most brain areas showing group differences were negatively correlated with the duration of heroin use except for the cerebellum and BA13 (Table 3). The same results were found whether or not age, education and gender were included as control variables. The partial correlation analysis between DGM and the abstinence time did not reveal any significant effect in all the above regions.

4. Discussion

Our optimized VBM analyses of this relatively large sample of participants clearly indicate a reduction in DGM in the prefrontal, anterior cingulate, insular and temporal cortices. This observation is consistent with the results from previous studies which showed structural abnormalities in these brain regions in heroin-dependent individuals (Lyoo et al., 2004, 2006). However, there is a remarkable difference between the present work and previous

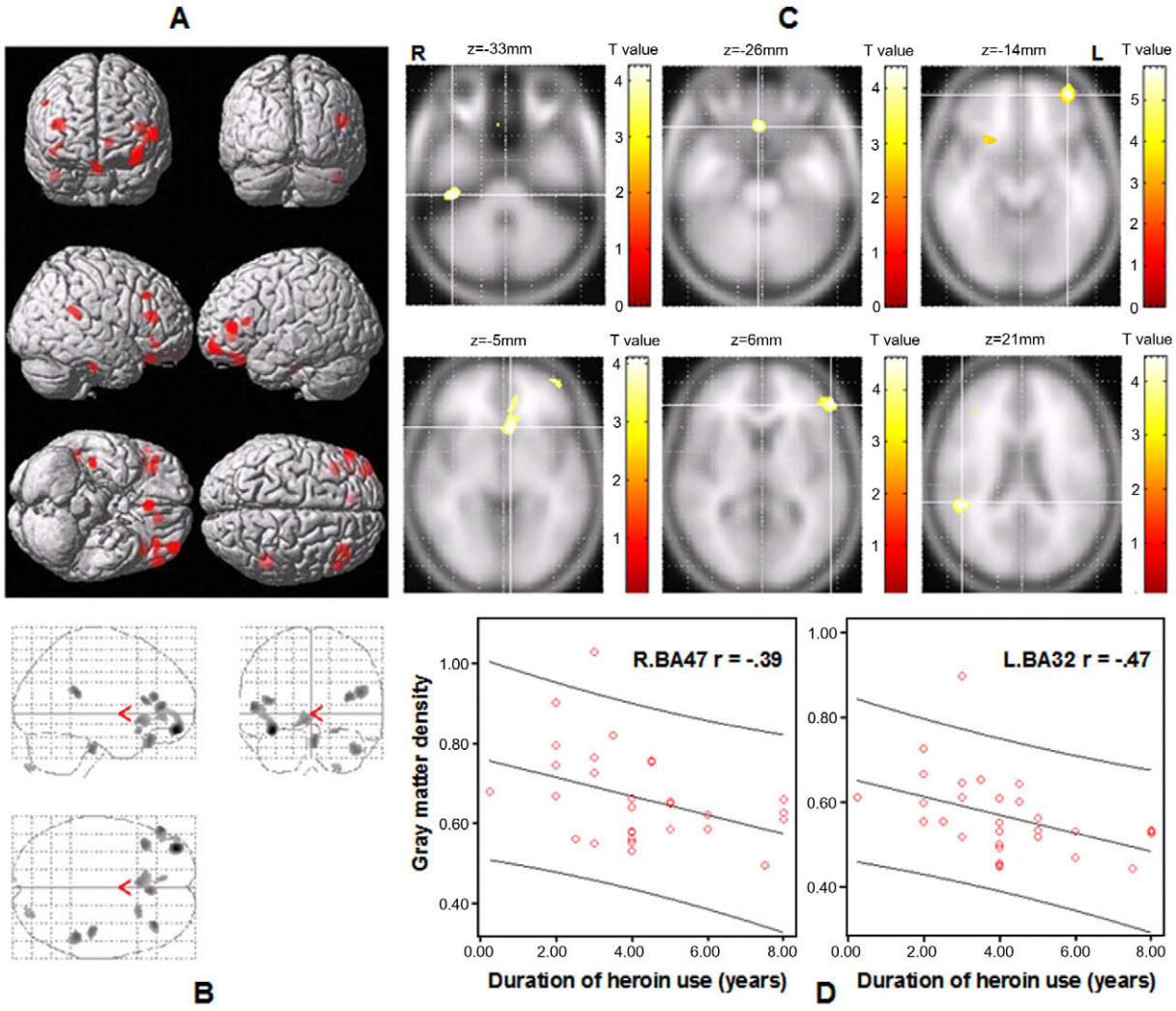

Fig. 1. Gray matter density in heroin-dependent individuals compared with the healthy subjects. Gray matter density decreases in the bilateral prefrontal cortex and temporal cortex of heroin-dependent individuals, depicted in the whole-brain rendering (A). Gray matter density decreases in the prefrontal, temporal, and insular cortices of heroin-dependent individuals depicted in the perspective whole-brain rendering (B). Gray matter density decreases in the prefrontal, temporal, and insular cortices of heroin-dependent individuals, depicted on the axial plane (C). The correlation between gray matter density and duration of drug use in BA32 (left, $r = -.47$, $p < 0.05$) and BA47 (right, $r = -.39$, $p < 0.05$) (D).

Table 2
Regions showing decreased gray matter density in the addiction group compared with the healthy group.

Talairach coordinates (*x*, *y*, *z*)	Brain region	BA	*t*-score	Cohen'd
−37, 54, −15	Left middle frontal gyrus	BA10	5.84	0.4
−55, 40, 5	Left inferior frontal gyrus	BA45	4.64	0.53
47, −39, 20	Right insula	BA13	4.47	0.64
35, 33, 16	Right inferior frontal gyrus	BA46	4.46	0.44
3, 29, −25	Right straight gyrus	BA11	4.46	0.56
−41, 24, 13	Left insula	BA13	4.39	0.51
42, −26, −34	Right fusiform gyrus	BA20	4.27	0.41
−5, 19, −6	Left anterior cingulate	BA25	4.12	0.35
23, 19, −7	Right inferior frontal gyrus	BA47	3.96	0.41
−8, 41, −1	Left anterior cingulate	BA32	3.82	0.4
28, −86, −53	R cerebellum	–	3.75	0.39

studies. In most of the previous studies, heroin-dependent individuals had substantial comorbidities of other psychoactive drugs, such as cocaine, marijuana, and alcohol (e.g., Lyoo et al., 2004, 2006; Rose et al., 1996). In contrast, none of the subjects in the present study was a current and lifetime users of other psychoactive drugs, except heroin and nicotine. Notably, the heroin-dependent individuals in almost all previous studies were also alcohol users, whereas none of our subjects was a life long alcohol user. Furthermore, unlike in most previous studies, none of our subjects had received or were receiving methadone replacement treatment.

Age effect may also contribute to the outcomes of brain structural measures (e.g., Good et al., 2001b). To minimize this effect, we recruited the participants younger than those in most of the previous studies (e.g., Gabryelak, Akahori, Przybylska, Józwiak, & Brichon, 2002; Lyoo et al., 2004, 2006) and with a narrow range of age (25 ± 2.4 years). Indeed, with conventional correlation analysis, we did not find any significant correlations between age and DGM in any brain regions in both the healthy and heroin-dependent groups, indicating that age effect was well controlled in the current study. Abstinence duration was also reported to influence the measurement of brain structural changes associated with drug use. For example, Kim et al. (2006) showed that the frontal decreased gray matter density of short-term abstinent methamphetamine abusers was more significant than short-term abstinent abusers. Other studies with opiate-dependent individuals with different abstinence conditions reported conflicting results (Lyoo et al., 2004, 2006; Pezawas et al., 1998; Reid et al., 2008; Rose et al., 1996). This inconsistency thus was at least partially due to the variation of abstinence conditions among these studies. To better control for the abstinence effect, we included this variable into partial correlation analysis. Furthermore, we also carefully selected the subjects presented with a narrow range of abstinence duration (4.93 ± 1.04 months). Although the gender difference was reported to contribute to gray matter changes in a large healthy sample (Good et al., 2001b), this sex specific effect was not observed in both the healthy and heroin-dependent groups.

Another important finding of the present study was that the duration of heroin use was correlated negatively with DGM in most of brain regions identified by group comparisons, even after other possible confounding factors, such as alcohol consumption, cigarette smoking, and abstinence time of heroin use, were controlled. The correlations between duration of heroin use and DGM have not been previously reported by studies of opiate dependence, although a similar result was found in several studies with users of other drugs (Matochik, Eldreth, Cadet, & Bolla, 2005; Sim et al., 2007). For example, Sim et al. (2007) reported negative correlations between duration of cocaine use and DGM in cocaine users. Similarly Matochik et al. (2005) observed a negative correlation between duration of marijuana use and white matter concentration (but not gray matter concentration).

The negative correlation between duration of heroin use and DGM suggests that heroin use has a cumulative effect; the longer the heroin use, the lower the level of DGM. This is in agreement with previous behavioral study showing a negative correlation between duration of heroin use and performance in a stop-signal task (Monterosso, Aron, Cordova, Xu, & London, 2005). Hence, early intervention is particularly important for the treatment of heroin addiction.

The current observation of structural abnormality in the prefrontal and anterior cingulate regions is consistent with previous behavioral and fMRI studies showing impaired cognitive function and increased impulsiveness along with changes of activation in the prefrontal-cingulate network in heroin users (Forman et al., 2004; Galynker et al., 2007; Kirby, Petry, & Bickel, 1999; Lee & Pau, 2002; Lee et al., 2001, 2005; Ornstein et al., 2000; Rotheram-Fuller, Shoptaw, Berman, & London, 2004; Xiao et al., 2006). This network also plays a critical role in cognitive function in healthy subjects (Cole & Schneider, 2007; Stevens, Kiehl, Pearlson, & Calhoun, 2009).

Our observation of the decreased GMD in the temporal regions as well as in the left BA 45 may account for memory impairments and spatial deficits in heroin-dependent individuals as reported in the previous studies (Ersche et al., 2006; Ornstein et al., 2000; Prosser et al., 2006; Wang et al., 2007), as these regions are believed to play an important role in semantic memory (e.g., Booth, Charette, & Persinger, 2002; Friederici, Opitz, & von Cramon, 2000; Lee & Pau, 2002; Zhu et al., 2009). Interestingly, the structural abnormality in these regions was also observed in dependence of other drugs, such as methylenedioxymeth-amphetamine (MADA) (Cowan et al., 2003), suggesting that different psychoactive drugs may produce possible damage in those common brain regions.

We also observed decreased DGM in the insula cortex in heroin-dependent individuals. This region was shown to involve processing self-induced and/or internally generated recalled emotions (Lee et al., 2005) and several functional brain imaging studies have reported activation in the insula when opiate (Daglish et al., 2003), alcohol (Mechtcheriakov et al., 2007), and marijuana (Tapert et al., 2007) users were exposed to environmental cues, which could induce craving. Hence, decreased DGM in the insula may result in less efficient emotion regulation in heroin-dependent individuals, leading to a hypersensitivity to cues for drug craving. However, there might be another account for structural changes in the insular cortex. The insula was recently shown to be as an important anatomical basis for nicotine dependence (Naqvi, Rudrauf, Damasio, & Bechara, 2007). Since our heroin-dependent subjects were also cigarette smokers, insular impairment observed in the present

Table 3
Partial correlation between duration of heroin use and gray matter density.

L.BA10	L.BA45	R.BA11	R.BA46	R.BA47	L.BA32	L.BA25	R.BA20	L.BA13	R.BA13	Cerebellum
−.49**	−.49**	−.40*	−.36#	−.39*	−.47**	−.43*	−.42*	−.42*	−.24	−.29

Note: Partial correlation analysis controlled age of first use, abstinence time, smoking and alcohol consumption.
* $p < 0.05$.
** $p < 0.01$.
\# $p = 0.07$.

study may be strengthened by nicotine use even though nicotine use was included as a covariate in our analysis. It should be mentioned that DGM of the right insular cortex did not significantly correlate with the duration of heroin use in partial correlation analysis, while the left insular cortex did, although the DGM of both sides of the insular cortex was lower in heroin-dependent individuals than in the healthy subjects. These results suggest that the left and right insula may play a differential role in drug dependence (Daglish et al., 2003; Wang et al., 1999). Further study is needed to confirm this speculation.

We also found significant DGM decrease in the heroin-dependent subjects in the cerebellum, while no significant correlation was detected between DGM of this structure and the duration of heroin use. This may be due to the use of partial correlation analysis, in which effect of nicotine use was controlled. Cigarette smoking alone was reported to inversely correlate with the cerebellar volume (Gallinat et al., 2006).

It is should be noted that Reid et al. (2008) reported reduction of gray matter in the thalamus. However, our present study did not find any difference in this region between heroin-dependent individuals and healthy subjects. The discrepancy was unlikely due to weak statistical power in the present study, as our sample size was larger than that adopted by Reid et al. (2008) (30 heroin-dependent subjects in the present study while nine in Reid et al.'s study) and both studies used optimized VBM, a powerful brain structural analysis method recently developed. One of the possible reasons, as suggested by Reid et al. (2008), is that the reduced thalamus associated with heroin dependence might be influenced by alcohol use. This interpretation appears consistent with previous studies showing that alcohol dependence caused decreased thalamus gray matter (Kril, Halliday, Svoboda, & Cartwright, 1997), and alcohol-related cues elicited activation in the thalamus in alcoholic subjects (George et al., 2001). In our study, none of the subjects were life long alcohol users.

There are several limitations which should be considered in interpreting our findings. First, since heroin-dependent individuals in the present study have used nicotine, our results might be confounded. In view of this, we employed the covariate procedure in the partial analysis. Second, although we did not find any significant relationships between abstinence duration and changes of DGM, this correlation cannot be ruled out completely. Third, gender and handedness effects on brain structural changes in heroin-dependent individuals remain open questions for further studies.

In conclusion, with a relatively large sample, we observed decreased DGM in lifetime heroin-dependent individuals, with less comorbid use of other psychoactive drugs, particularly alcohol and cocaine, which were present in almost all previous studies. Furthermore, a negative correlation between duration of drug use and DGM was observed. These results provide more compelling evidence for brain structural changes in heroin-dependent individuals.

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