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ORIGINAL INVESTIGATION

Dopamine transporter availability in heroin-dependent subjects and controls: longitudinal changes during abstinence and the effects of Jitai tablets treatment

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Abstract
Rationale Previous imaging studies have indicated that the levels of the dopamine transporter (DAT) are reduced in the brains of heroin users. However, whether these changes can be reversed by abstinence and/or treatment remains unclear.
Objectives This study aims to investigate DAT availability in heroin users and changes in DAT availability after abstinence and treatment with the Jitai tablets, a traditional Chinese medicinal product that is approved for the treatment of opioid addiction.
Methods Single-photon emission computed tomography (SPECT) with [^{99m}Tc] TRODAT-1 was performed on heroin-dependent patients (n=64) and healthy controls (n=15). The patients were randomly assigned to treatment with either placebo or the Jitai. All patients underwent SPECT imaging both at baseline and after 6 months of treatment. DAT availability was assessed in the caudate and putamen. Depression and anxiety were evaluated at baseline.
Results DAT availability remained at low levels during a 6-month period in the placebo-treated group but was increased (14–17 %) in the Jitai-treated group. The ratio of DAT availability at month 6 to that at baseline in the Jitai-treated group was significantly higher than that in the placebo-treated group in both the bilateral caudate and putamen. DAT uptake in the striatum was significantly correlated with daily heroin dose, years of heroin use, and depression.
Conclusions These findings suggest that chronic heroin use induces long-lasting striatal DAT reductions. DAT availability remained unchanged during a 6-month period of abstinence. Treatment with Jitai appears to be effective at increasing striatal DAT availability.

Keywords Dopamine transporter · Heroin dependence · Single-photon emission computed tomography · Jitai tablets

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Introduction

Opioid addiction represents a significant global public health problem. The World Drug Report of 2011 states that there are 12 to 21 million opiate users worldwide, of which approximately 75 % are heroin users (UNODC 2011). Dopaminergic neurons and their projections are important neural substrates that have been implicated to play a role in opioid addiction (Chang et al. 1997; Nestler 2005). Acute administration of opioid drugs activates the brain dopaminergic neurons and increases striatal dopamine (DA) release (Di Chiara and Imperato 1988; Wise et al. 1995), while chronic opioid use leads to a variety of changes, such as the downregulation of DA transporters and receptors and the dysregulation of DA functions (Kish et al. 2001; Shi et al. 2008). Degeneration of

the DA system is thought to contribute to the intense drug cravings that can persist even after a long period of abstinence and relapse (Nestler 2005).

The dopamine transporter (DAT) protein is located primarily on the presynaptic membranes of dopaminergic neurons and modulates the reuptake of dopamine from the synaptic cleft. Decreased DAT levels that are caused by the chronic use of stimulants, such as methamphetamine and cocaine, have been well documented (Fleckenstein et al. 2000; Volkow et al. 2001b; Wilson et al. 1996; McCann et al. 2008). However, relatively few studies have investigated the association between DAT function and opioid addiction. Earlier research in this area was either performed primarily in rodents (Sklair-Tavron et al. 1996) or by postmortem evaluations in humans (Kish et al. 2001). More recently, molecular imaging methods have been applied to the study of DAT availability in rhesus monkeys that were exposed to morphine (Xiao et al. 2006) and in human heroin users (Shi et al. 2008; Jia et al. 2005; Yeh et al. 2012; Cosgrove et al. 2010). Most, but not all, of these studies have indicated that opioid addiction is associated with reductions in DAT. Hence, controversy remains as to the status of the DAT in chronic heroin users. Furthermore, whether reductions in brain DAT can be reversed after sustained abstinence and/or drug treatment remains unknown. Such knowledge would clearly be important for understanding the pathophysiology underlying opioid addiction and could be valuable for the development of effective treatment strategies.

At present, drugs that are aimed at reducing the severity of withdrawal symptoms are themselves opiates (i.e., methadone), which allow for the gradual removal of the narcotic from the brain, thereby reducing the intensity of withdrawal symptoms, even if the drugs are considered to be highly addictive themselves (Gonzalez et al. 2002). Methadone has been reported to cause reductions in DAT levels in the brain during maintenance treatment. Subjects that have been treated with methadone are observed to have lower DAT availability when compared with subjects who have undergone prolonged periods of abstinence (Shi et al. 2008). In light of the important role of the DA system in addiction, one avenue for treatment may be to develop and test drugs that can repair alterations in the DA system while reducing withdrawal symptoms. To our knowledge, no medicine that is effective at reversing the decreased levels of DAT in the brains of heroin users has been tested in double-blind trials to date.

Traditional medicines have recently received wide attention in the treatment of drug addiction. Several studies have highlighted the efficacies of medicinal herbs for reducing ethanol, nicotine, and opioid dependence (Gupta and Rana 2008; Mattioli et al. 2012; Lu et al. 2009). The Jitai tablets, a traditional Chinese medicinal product, have been approved since 2004 for the treatment of opioid addiction by the Chinese State Food and Drug Administration. It is prepared from a traditional Chinese herbal prescription that has been used for approximately 150 years in the treatment of opiate addiction. The prescription is comprised of 15 herbs, including *Rhizoma Corydalis* (10.2 % in the prescription), *Flos Daturae* (2.2 % in the prescription), and *Radix ginseng* (2.2 % in the prescription), among others. The various components or active ingredients in the Jitai tablets have recently been identified (Wang et al. 2010, 2012). In addition to sedation, tranquilization, and body toxin removal, some of the herbs and components of the Jitai tablets prescription have been proven to be effective in improving withdrawal symptoms and preventing relapse in heroin-dependent patients or animals (Yang et al. 2008; Xiang et al. 2006; Lee et al. 2011). L-Tetrahydropalmatine (L-THP) (20 μg in each Jitai tablet), an active component of *Rhizoma Corydalis*, can reduce heroin cravings and increase the abstinence rate among heroin-dependent patients (Yang et al. 2008). Scopolamine (70 μg in each Jitai tablet), the major chemical component of Flos Daturae, has been shown to mitigate the withdrawal symptoms that are associated with opiate addiction (Xiang et al. 2006). Ginseng, with its various ginsenosides, was reported to inhibit anxiety and depression responses that result from morphine withdrawal (Lee et al. 2011). Previous clinical trials have demonstrated that treatment with the Jitai tablet is efficacious at inhibiting withdrawal symptoms and rehabilitating the abnormal physiology that is induced by chronic drug use (Li et al. 2007; Xu et al. 2000). However, whether protracted treatment is effective at repairing reductions in the DA system remains unknown.

The present study was conducted to investigate DAT availability in detoxified heroin users, changes in DAT availability after heroin abstinence, and the effects of treatment with the Jitai tablets on DAT levels in the brain after 6 months of treatment. Heroin-dependent subjects are known to exhibit negative moods when heroin use is discontinued. We further assessed the relationship between striatal DAT uptake function and depression/anxiety. Heroin-dependent subjects were administered Jitai tablets in a double-blind trial and underwent single-photon emission computed tomography (SPECT) imaging with the DAT radiotracer [^{99m}Tc] TRODAT-1 at two time points: a baseline scan that was taken after the initial stage of abstinence and a second scan that was taken after 6 months of treatment.

Methods

Subjects

Heroin-dependent subjects Sixty-four heroin-dependent subjects (58 males and 6 females) were recruited at the Drug

Rehabilitation Center, Shanghai, China. The characteristics of these subjects are presented in Tables 1 and 2. The inclusion criteria were as follows: (1) aged 18 to 55 years, (2) met the DSM-IV criteria for opioid dependence, (3) a positive urine morphine test, (4) the last heroin use occurred 8–36 h prior to recruitment, and (5) cocaine and other drug use was absent. The exclusion criteria were as follows: (1) current or past psychiatric illness other than heroin dependence, (2) neurological signs and/or history of neurological disease (e.g., Parkinson's disease or other movement disorders), (3) history of head trauma, and (4) history of cardiovascular, endocrine, or other serious physical diseases.

Healthy controls Fifteen healthy subjects (13 males and 2 females) were recruited through newspaper advertisements and flier postings. None of the subjects had a history of drug use, such as heroin, methamphetamine, MDMA, cannabis, and/or alcohol. The exclusion criteria were the same as they were for the heroin-dependent subjects.

Written informed consent was obtained from each subject. The study was approved by the Shanghai Mental Health Center, Shanghai, China.

Study design

The study was a randomized, double-blind, placebo-controlled trial of Jitai tablets treatment. The drugs were numbered using a completely randomized sequence that was generated by an independent third party using a protected computer database containing the randomization list. All of the other study personnel were blinded to the treatment assignments throughout the duration of the study. Prior to randomization, all of the patients completed a detoxification protocol, during which time they were given Jitai tablets (four tablets three times daily for the first 5 days and two tablets three times daily for the following 5 days), and had a washout period of at least 5 days. After 15–18 days of detoxification, heroin-dependent patients were randomly assigned to treatment with either placebo or Jitai tablets in accordance with the order of drug numbering. The patients then received the Jitai tablets or placebo from clinicians at oral doses of three tablets twice daily for the first 3 months and two tablets twice daily for the subsequent 3 months. The patients were monitored by physicians to confirm abstinence from illicit drug use during the study period. All of the patients undergoing treatment at the rehabilitation center agreed to comply with the center's strict regulations regarding the discontinuation of illicit drug use. The patients lived, ate, and conducted all other daily activities at the center, and received all necessary supplies from the center's supply store. If the patients had to leave the facility, they were accompanied by the physicians or staff members. Any items that were brought into the facility by the patient's families or friends were inspected by the staff to ensure that the items did not contain illicit drugs. Physical examinations were performed and the blood and urine chemistries were analyzed at baseline and during treatment after months 1, 3, and 6.

SPECT imaging procedure

The levels of brain DAT availability were assessed using SPECT imaging with the radiotracer [^{99m}Tc] TRODAT-1 (a radiolabeled form of a tropan derivative that is used for labeling DAT). SPECT imaging was performed as previously described, with minor modifications (Kung et al. 1996). Each subject received 740 MBq (20 mCi) of [^{99m}Tc] TRODAT-1 (purity >90 %) intravenously. Approximately 3 h after tracer injection, static SPECT brain imaging was performed on a Siemens NME.CAM Gantry double detector scanner with

Table 1 Demographic characteristics of all of the heroin-dependent subjects and healthy controls

	Heroin-dependent subjects					Healthy controls		
	All (n=64) Mean (SD)	Jitai (n=25)	Placebo (n=30)	t (df=53)/chi-square	p value[a]	(n=15) Mean (SD)	t (df=77)/chi-square	p value[b]
Male/female	56/8	24/1	24/6	3.143	0.076	13/2	0.008	0.930
Age, years	37.0 (8.8)	36.0 (8.0)	38.0 (8.7)	−0.840	0.405	32.5 (7.3)	1.836	0.070
BMI, kg/m^2	21.1 (3.0)	20.8 (3.3)	21.3 (3.0)	−0.615	0.541	23.1 (1.5)	−2.554	0.013
Duration, years	7.3 (4.1)	7.3 (4.2)	7.4 (3.6)	−0.094	0.926			
Dose, g/d	0.9 (0.6)	0.9 (0.6)	1.0 (0.5)	−0.485	0.630			
Intake, no. (snorting/injection/both)	34/24/6	12/12/1	16/9/5	3.293	0.198			

t test for continuous variables; chi-square test for categorical variables

BMI body mass index

[a] Jitai vs. placebo

[b] All heroin-dependent subjects vs. healthy controls

Table 2 Demographic characteristics of the final sample in the second SPECT imaging session

	Jitai (n=18)	Placebo (n=25)	t (df=41)/chi-square	p value[a]
Male/female	17/1	20/5	1.819	0.177
Age, years	34.5 (8.0)	38.4 (8.9)	−1.486	0.145
BMI, kg/m^2	21.6 (2.6)	22.3 (2.5)	−0.988	0.329
Duration, years	6.8 (4.0)	8.1 (3.3)	−1.197	0.238
Dose, g/d	0.9 (0.6)	1.0 (0.5)	−0.458	0.649
Intake, no. (snorting/injection/both)	11/6/1	11/9/5	2.185	0.335

BMI body mass index

[a]*t*-test for continuous variables; chi-square test for categorical variables

high resolution fan beam collimators (Siemens, Erlangen, Germany). Brain images were acquired in a 128×128 matrix with a 1.0 zoom over a circular 360° rotation. Transverse images were reconstructed using a Metz filter with a cutoff of 0.55 Nyguist and an order of 15. An attenuation coefficient of μ=0.12 cm^{-1} was used according to Chang's first-order method (Chang 1978). The transverse image thickness was 4.0 mm (1 pixel). In each patient, data were evaluated in the four consecutive transverse slices showing the highest tracer accumulation in the basal ganglia. Regions of interest (ROIs) were drawn bilaterally over the caudate and putamen regions by an experienced nuclear medicine physician, who was blinded to the group conditions and clinical information and had been previously trained and achieved high reliability (>0.95). Magnetic resonance imaging (nonregistered) was used as a rough guide for defining the caudate nucleus, putamen, and occipital cortex (OC) in the SPECT images. Mean activity in the caudate nucleus and putamen was calculated by subtracting the mean counts per pixel in the OC as background from the mean counts per pixel in the caudate nucleus or putamen regions and dividing the result by the mean counts per pixel in the OC: [(Target−OC)/OC] (Huang et al. 2001; Felicio et al. 2010). Imaging procedures were conducted for heroin-dependent subjects at two time points: following the initial period of abstinence (baseline, post-detoxification, an average of 20 days after last heroin use) and posttreatment (an average of 20 days after receiving the last Jitai tablets or placebo).

Psychiatric assessment

Because heroin-dependent subjects are known to exhibit negative moods when heroin use is discontinued, we included assessments of the Hamilton Depression Rating Scale (HAMD) (Hamilton 1960) and the Hamilton Anxiety Rating Scale (HAMA) (Hamilton 1959). The HAMD and HAMA scores were assessed prior to the first SPECT imaging session and correlations between DAT levels in the striatum and depression or anxiety were determined.

Statistical analysis

Means (SD) and proportions were calculated for the baseline characteristics by groups. The differences in population characteristics among the different groups were compared via t test for continuous variables or via chi-square test for categorical variables. Pearson's correlation coefficient was used to compare the correlations between DAT binding and the dose of heroin consumed, years of heroin use, or rating scale scores.

Multivariable regression models were applied to compare DAT availability between heroin-dependent subjects and healthy controls, with or without adjustment for the major baseline characteristics. For the randomized controlled trials, changes in DAT availability after 6 months of treatment were expressed as the ratio of dopamine transporter availability at month 6 to that at baseline. These ratios were applied as the primary outcome. DAT availability before and after treatment was compared using the paired t test. Multivariable regression models were applied to compare the DAT availability ratios in different areas (caudate or putamen) and positions (right or left) among the different groups, with adjustments for baseline dopamine transporter availability. Due to the "repeated" characteristics of the two variables (area and position), mixed-model repeated measures analysis (Proc Mixed), with the subjects set as random effects, was also used to evaluate the effects of Jitai treatment on the DAT availability ratio. The compound symmetry was constructed as the covariance structure. All of the statistical analyses were performed in SAS 8.2 (SAS Institute, Cary, NC, USA).

Results

Participants

A total of 64 heroin-dependent subjects were recruited to the study, along with 15 healthy subjects. Nine heroin users declined to participate in treatment after the first SPECT imaging session. As a result, a total of 55 heroin-dependent subjects were randomized for participation in the treatment trial and included in the baseline imaging analysis. A further 12 heroin-dependent subjects (five in the placebo group and seven in the Jitai group) dropped out of the study during the treatment phase because they left the rehabilitation center. Ultimately, 43 subjects completed all of the procedures in the study. Subject characteristics are shown in Tables 1 and 2.

There were no significant differences in the demographics between the heroin-dependent subjects and healthy controls, with the exception of BMI. There were no significant differences in the demographics for the heroin-dependent subjects in the placebo- and Jitai-treated groups both before and after treatment.

SPECT imaging analysis

Significantly lower DAT availabilities (an approximately 28–34 % decrease) in the bilateral caudate nucleus and bilateral putamen were observed in the heroin-dependent subjects compared to the healthy controls (Table 3 and Fig. 1). Because the estimates of DAT availability in the right caudate/putamen were highly consistent with those in the left caudate/putamen ($r>0.70$, $df=63$, $p<0.001$), we averaged these two measures into one caudate/putamen value for the correlation analysis. Significant negative correlations were observed between the years of heroin use and DAT availability in both the caudate and putamen ($r=0.304$, $df=63$, $p=0.015$; $r=0.265$, $df=63$, $p=0.034$). There was also a significant negative correlation between the average daily heroin dose and DAT availability in the caudate and putamen ($r=0.279$, $df=63$, $p=0.026$; $r=0.302$, $df=63$, $p=0.010$) (Fig. 2). These findings suggest that a longer duration and higher daily dose of heroin use are associated with more pronounced reductions in DAT availability. In addition, DAT levels were significantly correlated with HAMD scores in both the caudate and putamen ($r=0.314$, $df=55$, $p=0.019$; $r=0.274$, $df=55$, $p=0.041$), but no correlations were found between DAT levels and HAMA scores in either area ($r=0.141$, $df=55$, $p=0.298$; $r=0.211$, $df=55$, $p=0.118$) (Fig. 2).

The results from two SPECT imaging sessions for the placebo-treated group and the Jitai-treated group are presented in Table 4. In the placebo group, DAT availability remained reduced during abstinence. No significant differences were found between the baseline and second imaging scans, although small decreases in the right caudate and bilateral putamen were observed ($p>0.05$). Therefore, we inferred that DAT availability in the placebo group remained unchanged during the 6-month study period. In the Jitai-treated group, DAT availability after 6 months of treatment was higher than that at baseline. In particular, DAT levels were significantly higher than baseline in the left caudate. The differences in DAT availability between the Jitai-treated group and the healthy controls decreased over time, although significantly lower levels of DAT were still observed in the heroin-dependent subjects. When compared with the placebo group, the Jitai tablets-treated patients had significantly higher levels of DAT in the bilateral putamen and the left caudate after 6 months ($p<0.05$). The ratios of dopamine transporter availability at month 6 compared to those at baseline in the Jitai-treated group were significantly higher than those in the placebo-treated group in both the bilateral caudate and the bilateral putamen after adjustment for baseline dopamine transporter availability ($p<0.05$). Mixed-model repeated measures analysis with the subjects set as random effects was also used to evaluate the effects of Jitai treatment on the dopamine transporter availability ratios. The results indicated that Jitai treatment increased DAT availability compared to the placebo ($p=0.005$). The effects of treatment on the different areas (caudate vs. putamen, $p=0.733$) or positions (right vs. left, $p=0.926$) did not differ in a statistically significant manner.

Discussion

To our knowledge, the Jitai tablets is the first drug that has been reported to be effective at restoring DAT levels in heroin users, as demonstrated in this randomized, placebo-

Table 3 Comparison of dopamine transporter availability between heroin-dependent subjects ($n=64$) and healthy controls ($n=15$)

	DAT	Unadjusted			Adjusted[a]		
	Mean (SD)	β	SE	p	β	SE	p
Caudate, right							
Healthy control	2.00 (0.44)	Ref			Ref		
Heroin-dependent subjects	1.32 (0.22)	−0.67	0.08	<0.001	−0.67	0.08	<0.001
Caudate, left							
Healthy control	1.90 (0.38)	Ref			Ref		
Heroin-dependent subjects	1.30 (0.22)	−0.60	0.07	<0.001	−0.59	0.08	<0.001
Putamen, right							
Healthy control	1.88 (0.41)	Ref			Ref		
Heroin-dependent subjects	1.31 (0.21)	−0.57	0.07	<0.001	−0.57	0.08	<0.001
Putamen, left							
Healthy control	1.81 (0.37)	Ref			Ref		
Heroin-dependent subjects	1.30 (0.22)	−0.51	0.07	<0.001	−0.49	0.08	<0.001

DAT dopamine transporter

[a]The regression model was adjusted for age and body mass index

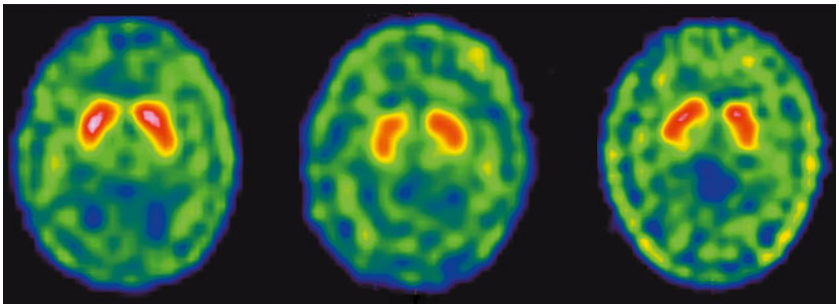

Fig. 1 Activity distribution of [^{99m}Tc] TRODAT-1 in the brains of a healthy control (*left*) and a heroin-dependent subject before (*middle*) and after 6 months of treatment (*right*)

controlled, double-blind trial. The results of the present study support previous reports that chronic heroin use induces reductions in striatal dopamine terminals, as evidenced by decreases in DAT availability. By strictly controlling the duration of heroin abstinence, we observed that DAT availability remained at reduced levels without reversion in the placebo-treated group, but increased significantly in the Jitai-treated group after 6 months. In addition, in heroin-dependent subjects, DAT availability was negatively correlated with the duration and daily dose of heroin use, as well as HAMD scores. In contrast, HAMA scores were not observed to be negatively correlated with DAT availability.

Three previous imaging studies have documented reduced striatal DAT levels in heroin-dependent subjects compared to healthy controls (Shi et al. 2008; Jia et al. 2005; Yeh et al. 2012). The results of the current study are consistent with the findings of these three imaging studies and are also in agreement with the findings of a study of rhesus monkeys in which morphine exposure was shown to be associated with a decrease in striatal DAT (Xiao et al. 2006). However, a different imaging study (Cosgrove et al. 2010) and a postmortem study that was conducted in humans (Kish et al. 2001) reported no significant differences in striatal DAT levels between heroin users and healthy controls. One notable difference among these studies is that the heroin-dependent subjects in the present study, as well as those in the studies conducted by Jia et al. and Shi et al., were detoxified for a minimum of 10 days prior to the first imaging session, whereas Cosgrove et al. and Kish et al. studied active heroin users. Another difference among the human studies is the sample size: studies reporting positive findings of decreased DAT levels in heroin-dependent subjects tended to have a larger number of enrolled subjects, while studies reporting negative findings (Kish et al. 2001; Cosgrove et al. 2010) tended to have smaller sample sizes, which may have limited their statistical power to detect changes in striatal DAT.

Injury of the DA transmission system may have negative implications for the experience of pleasure and reward, leading to a state of depression or anxiety, which could be a vulnerability factor for the development of addiction and relapse (Gerra et al. 2000; Volkow et al. 2006; Zijlstra et al. 2008). We found a significant correlation between DAT availability and HAMD scores in heroin users, indicating

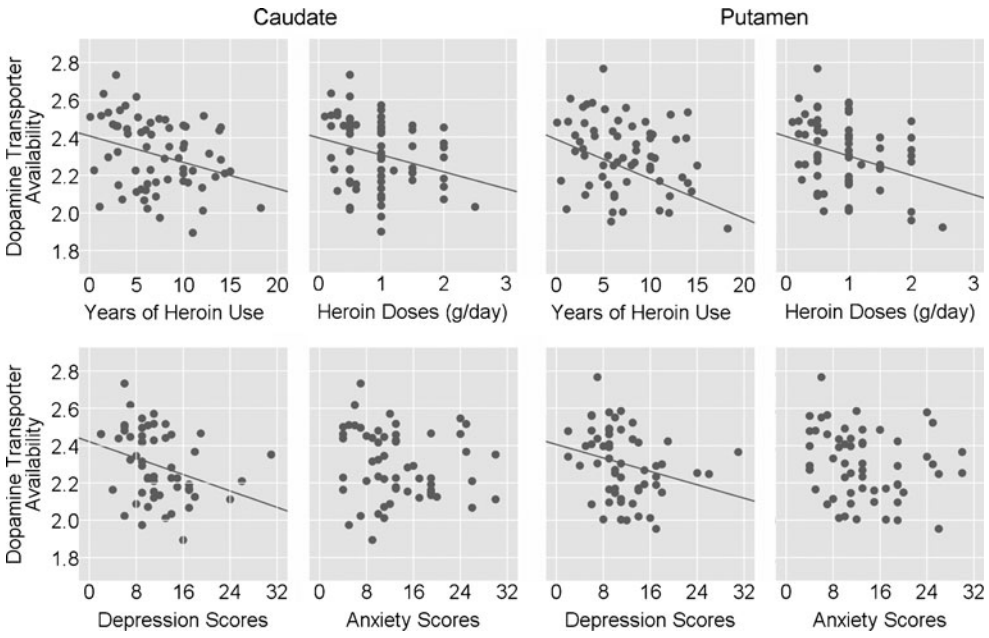

Fig. 2 Correlation between dopamine transporter availability ([^{99m}Tc] TRODAT-1 specific uptake) and years of heroin use, daily heroin dose, depression scores, or anxiety scores in heroin-dependent subjects

Table 4 Comparison of dopamine transporter availability between the placebo-treated and Jitai-treated groups before and after treatment

	DAT at baseline[a]	DAT at baseline[b]	DAT after 6 months[b]	Ratio of the DAT at month 6 to baseline[b]	Difference in the change of DAT by groups[c]		
	Mean (SD)				β	SE	p
Caudate, right							
Placebo	1.33 (0.21)	1.33 (0.20)	1.30 (0.30)	0.98 (0.21)	Ref		
Jitai	1.32 (0.25)	1.32 (0.27)	1.48 (0.27)	1.15 (0.24)$^{\#}$	0.16	0.06	0.016
Caudate, left							
Placebo	1.29 (0.19)	1.29 (0.18)	1.28 (0.35)	1.00 (0.33)	Ref		
Jitai	1.31 (0.24)	1.31 (0.23)	1.51 (0.28)*$^{\#}$	1.17 (0.23)	0.17	0.08	0.044
Putamen, right							
Placebo	1.32 (0.22)	1.33 (0.21)	1.24 (0.29)	0.96 (0.21)	Ref		
Jitai	1.31 (0.21)	1.30 (0.22)	1.47 (0.29)$^{\#}$	1.15 (0.24)$^{\#}$	0.20	0.06	0.005
Putamen, left							
Placebo	1.29 (0.16)	1.28 (0.15)	1.25 (0.34)	0.99 (0.32)	Ref		
Jitai	1.32 (0.25)	1.32 (0.26)	1.47 (0.27)$^{\#}$	1.14 (0.23)	0.17	0.08	0.035

DAT dopamine transporter

* $p<0.05$ (paired t test was significantly different from baseline); # $p<0.05$ (unpaired t test was significantly different from the placebo-treated group)

[a] $n=30$ in the placebo-treated group, and $n=25$ in the Jitai-treated group

[b] Patients who finished two scans, $n=25$ in the placebo-treated group and $n=18$ in the Jitai-treated group

[c] The regression model was adjusted for baseline DAT availability

that DAT reductions may underlie the depression observed in heroin users. The DAT is an important factor in the manifestation of negative mood.

We found no statistically significant differences in striatal DAT availability in the placebo-treated group between baseline and 6 months of abstinence. In comparison with healthy controls, DAT levels remained low during the 6-month treatment period. Previous imaging studies have evaluated DAT availability in users of various drugs, particularly psychostimulants such as cocaine and methamphetamine. In cocaine users, DAT levels appear to increase shortly after cocaine discontinuation and normalize after detoxification (Malison et al. 1998). Methamphetamine abusers tend to experience long-lasting decreases in DAT, and DAT levels recover very slowly after months of detoxification (McCann et al. 1998). The results of the present study demonstrate that decreased DAT levels in the brains of chronic heroin users are long-lasting and do not readily recover during abstinence. This finding further verifies the findings of previous reports that have deduced that differences in DAT levels in the brain change during the various stages of addiction and across different types of drugs of abuse (Volkow et al. 2001a). In addition, a recent report found that heroin addiction was associated with lower D_2 receptor binding and lower presynaptic dopamine (Martinez et al. 2012). Thus, it seems reasonable to conclude that chronic heroin use is associated with altered DA neurotransmission, which may contribute to the decreased sensitivity of addicted subjects to natural stimuli and, as such, predispose drug users to seek stimulation in order to temporarily remedy negative moods. More importantly, DAT availability remained at low levels after 6 months in the placebo-treated group. Long-term decreases in the DAT are consistent with the lasting presence of cravings and relapse. As a result, sustained decreases in DAT availability may play a crucial role in heroin relapse. Hence, treatment strategies that restore DAT levels may be valid and effective approaches to the prevention of relapse in opiate addiction.

Jitai tablets have been approved in China for the treatment of opiate dependence since 2004. Previous clinical trials have demonstrated that treatment with Jitai tablets is efficacious at inhibiting withdrawal symptoms, with no obvious adverse side effects or potential for the development of dependence (Li et al. 2007; Xu et al. 2000). Some patients may suffer from nausea, mild blurred vision, and dry mouth, but most patients do not require treatment and the symptoms tend to disappear after dose decrement or after subsequent treatment (Shi et al. 2006). In the present study, we demonstrated that Jitai tablets treatment increased DAT availability in heroin-dependent subjects. The ratio of the DAT availability at month 6 to that at baseline in the Jitai-treated group was significantly higher than that in the placebo-treated group in the bilateral striatum. Some herbs and components of the Jitai tablets have been reported to be effective in regulating the DA system in heroin-dependent patients or animals (Yang et al. 2008; Tsukada et al. 2000;

Kim et al. 1995). L-THP is an antagonist of DA receptors. Its antagonistic effect on DA receptors, particularly D_2 and D_3 receptors, may play an important role in reducing drug cravings (Yang et al. 2008). L-THP is also found to increase the synthesis and release of endogenous opioid peptides in the central nervous system, an action that may contribute to the anti-dependence potential of drugs of abuse (Chu et al. 2008). Scopolamine is effective at enhancing the dynamics of dopamine synthesis and DAT availability through the inhibition of muscarinic cholinergic neuronal activity (Tsukada et al. 2000). Ginseng, with its various ginsenosides, was reported to prevent the development of dopamine receptor supersensitivity that is induced by chronic morphine administration (Kim et al. 1995). Usually, traditional Chinese medicines act by targeting multiple biological systems and through multiple pharmacological mechanisms. The mechanism underlying the ability of the Jitai tablets to upregulate DAT levels in heroin users was likely due to the combined effects of some of the active ingredients, such as L-THP, scopolamine, and ginseng. Taken together, the Jitai tablets appear to be effective at reversing reduced DAT availability. However, further research is required to determine whether this effect plays a role in preventing relapse to heroin use

Some of the limitations of this study should be noted. First, this study lacked the evaluation on heroin cravings and relapse rates. Second, ROIs were manually drawn on the SPECT images. This is not a state-of-the-art technique to analyze SPECT images. Third, heroin-dependent patients are usually emaciated after long-term drug use. Thus, it is not surprising that there was a significant difference between the BMI values of the heroin-dependent and healthy subjects in the present study. Previous research has reported a negative correlation between DAT availability and BMI (Chen et al. 2008). However, in the present study, we found no correlation ($p>0.05$) between DAT availability and BMI in either the healthy controls or the heroin-dependent subjects. If healthy controls with matched BMIs had been enrolled, the differences in DAT availability between the heroin-dependent subjects and healthy controls should have been larger than that reported herein. Fourth, the heroin-dependent subjects were older than those in the control group (although not significantly). We found a negative correlation between age and DAT availability in the right caudate ($r=0.633$, $df=15$, $p=0.011$) and right putamen ($r=0.652$, $df=15$, $p=0.008$) in healthy controls, but no correlation in either the bilateral caudate or bilateral putamen of heroin-dependent subjects. Age-related reductions in DAT levels have been previously reported (Vandyck et al. 1995). According to published data, the 4-year average age difference in this study should not have impacted the results of the study. Meanwhile, the regression model was adjusted for both age and BMI. Fifth, no data were available regarding the smoking history of the subjects. Given the interaction of nicotine with the dopamine system, it may have been important to examine the smoking history of the subjects. Finally, because there were far more male heroin users than female heroin users in the rehabilitation center, we only recruited a small sample of female subjects and were unable to analyze sex-dependent effects of heroin use on DAT levels.

In conclusion, the results of the present study demonstrate that DAT availability is lower in the striatum of heroin-dependent subjects compared to healthy controls. We showed that DAT availability is negatively correlated with the duration and daily dose of heroin use, as well as HAMD scores. Importantly, we documented that the decreases in DAT are long-lasting and that no changes were evident during the 6-month study period in heroin-dependent subjects. Treatment with Jitai tablets increased striatal DAT availability. This is a highly significant result because it indicates that the Jitai tablets, as an approved treatment for heroin addiction, not only relieve withdrawal symptoms but may also rehabilitate brain DA function through increased DAT availability in abstinent heroin users. Although the exact mechanism(s) underlying this effect cannot be easily pinpointed, our study nonetheless provides the first concrete biological evidence of the benefits and efficacy of Jitai tablets in the treatment of opioid addiction.

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Conflict of interest All authors declare that they have no conflicts of interest.

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