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ORIGINAL INVESTIGATION

Longitudinal changes of dopamine transporters in heroin users during abstinence

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Abstract
Rationale Chronic exposure to heroin results in decreased dopamine transporter levels. Jitai tablets, a traditional Chinese medicine, have been effective at increasing striatal dopamine transporter availability after 6 months of treatment. However, it remains unknown how long the heroin-induced impairment persists and whether dopamine transporter can be normalized following long-term abstinence or treatment.
Objectives This study was to evaluate the time course of dopamine transporter changes in heroin users undergoing long-term abstinence and treatment with Jitai tablets for 1 year.
Methods Single-photon emission computed tomography using [^{99m}Tc]TRODAT-1 was performed on 64 heroin users and 20 healthy subjects to assess striatal dopamine transporter availability at baseline, 3, 6, and 12 months. Heroin users were randomly assigned to treatment with either placebo or Jitai tablets. Depression and anxiety scores were measured before each imaging session.
Results Compared with healthy controls, significant reduction in dopamine transporter availability was found in heroin users at baseline in both the right (by ~31.6 %) and left striatum (by ~33.2 %). At 6 months, dopamine transporter availability was significantly higher in Jitai tablet-treated group than placebo group in the bilateral striatum ($p<0.01$). At 12 months, dopamine transporter levels in both groups were upregulated substantially from baseline but still not recovered to normal levels in the left striatum ($p<0.05$). Depression and anxiety scores significantly decreased at 3, 6, and 12 months ($p<0.05$).
Conclusions Our results confirmed that heroin abuse induces pronounced, long-term reduction in dopamine transporter. Treatment with Jitai tablets appears to stimulate recovery.

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

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Introduction

Opioids top the list of illicit drugs that incur the most burdens of drug-related deaths worldwide. According to World Drug Report data, the users of opiates amount to 12.8 to 20.2 million globally (UNODC 2014), and opioids are the primary drug category implicated in overdose-related deaths (UNODC/WHO 2013). Drug abuse also places a heavy financial burden on society, with a total of US$200–250 billion expended on drug-related treatment worldwide (UNODC 2012). The dopamine (DA) system plays an important role in addictive behaviors, including opioid addiction (Di Chiara and Bassareo 2007). Upon acute administration, opioid drugs of abuse activate brain dopaminergic neurons as evidenced by

increased synaptic DA concentrations in the striatum (Dichiara and Imperato 1988; Rouge-Pont et al. 2002). Chronic opiate use leads to a variety of compensatory changes, such as reductions in DA transporters (DAT), DA receptors, and synaptic DA levels (Kish et al. 2001; Liu et al. 2013; Wilson et al. 1996). DAT is a key transmembrane protein that regulates DA reuptake from the synaptic cleft and is involved in the modulation of dopaminergic neurotransmission and the regulation of reward and dependence in drug addiction (Gainetdinov et al. 1998; Volkow et al. 1997). Findings from previous human imaging studies have indicated that changes in DAT exist extensively in users of various drugs of abuse. Long-lasting decreases in DAT were found in methamphetamine users (McCann et al. 1998; Volkow et al. 2001a), and recovery was very slow even after months of detoxification (Volkow et al. 2001b). In cocaine users, DAT levels increased shortly after cocaine discontinuation but normalized with detoxification (Malison et al. 1998). Chronic alcohol intake induced neuroadaptive reductions in striatal DAT availability, which were reversible during early abstinence (Heinz et al. 2004; Laine et al. 1999). Decreases in DAT availability have also been shown in tobacco and cannabis users (Leroy et al. 2012). However, findings on DAT level changes in opioid-dependent individuals are limited and inconsistent. For example, two human postmortem studies found a modest DAT reduction in the nucleus accumbens but not in the striatum (Kish et al. 2001), and a single-photon emission computed tomography (SPECT) imaging study found no association between long-term opioid exposure and reduced striatal DAT (Cosgrove et al. 2010). More recent preclinical and clinical studies, however, have provided consistent evidence for reduced DAT levels in opioid addiction (Gao et al. 2014; Jia et al. 2005; Liang et al. 2014; Liu et al. 2013; Shi et al. 2008; Yeh et al. 2012).

Certain first-line medications exist for the treatment of opioid addiction, including methadone, buprenorphine, naloxone, and naltrexone. These drugs have been shown to effectively alleviate opioid withdrawal symptoms. However, most of these drugs are also considered to be highly addictive themselves, and are ineffective at reversing the adaptive neurobiological changes (Gonzalez et al. 2002). Methadone maintenance treatment is effective at reducing heroin cravings (Leri et al. 2004), but one imaging study documented that subjects treated with methadone had significant and persistent decreases in DAT availability in the bilateral putamen compared with those in prolonged abstinence (Shi et al. 2008). Therefore, an urgent need still exists for more effective treatments that cannot only alleviate opioid withdrawal symptoms but also repair impairments in the DA system.

Traditional Chinese medicines (TCMs) have received wide attention as an alternative for the treatment of drug addiction (Liu et al. 2009). TCMs have been used for ~150 years in the treatment of opiate addiction. Jitai tablets (JTT) is one of the TCMs that have been approved since 2004 by the China Food and Drug Administration for treatment of opioid addiction. The prescription is composed of 15 herbs including Papaveraceae Corydalis (Yan hu suo), 10.20 %; Solanaceae Daturametel (Yang jinhua), 2.18 %; Lamiaceae Salvia Miltiorrhizae (Dan shen), 16.87 %; Araliaceae Panaxginsen (Ren shen), 2.18 %; Apiaceae Angelica sinensis (Dang gui), 10.20 %; Ranunculaceae Aconitum (Fu zi), 2.18 %; Myristicaceae Myristicacagayanensis (Dou kou), 2.18 %; Asteraceae Aucklandia (Mu xiang), 5.71 %; Thymelaeaceaceae Aquilaria, (Chen xiang), 4.35 %; Zingiberaceae Zingiber (Gan jiang), 2.18 %; Lauraceae Cinnamomum (Rou gui), 2.18 %; Semen Persicae (Tao ren), 10.20 %; Pearl powder (Zhen zhu fen), 13.47 % (Wang et al. 2012). Recently, 101 compounds contained in the JTT components and some of the putative active ingredients have been identified (Wang et al. 2010, 2012). Pharmacological effects for some of these compounds or components have been investigated in preclinical and clinical studies. For example, *L*-tetrahydropalmatine (*L*-THP) has been shown to be a DA antagonist, and its antagonistic effect on DA receptors may play an important role in reducing drug cravings (Yang et al. 2008). *L*-THP was also found to increase the synthesis and release of endogenous opioids in the central nervous system, an effect that may contribute to its anti-dependence potential (Chu et al. 2008). Scopolamine, another putative active ingredient in JTT, was effective at enhancing DA synthesis and DAT availability (Tsukada et al. 2000). Ginseng is another component in JTT, and its various ginsenosides have been reported to prevent the development of DA receptor supersensitivity induced by morphine (Kim et al. 1995). Previous clinical trials have documented the efficacy of JTT at inhibiting withdrawal symptoms and restoring the physiological functions altered by chronic drug use (Xu et al. 2000; Zihong et al. 2007). A prior study from our laboratory also documented that striatal DAT availability remained at reduced levels in heroin-dependent subjects during a 6-month period of abstinence, and treatment with JTT led to increased DAT after 6 months (Liu et al. 2013). However, whether striatal DAT levels can be normalized after longer period of abstinence, and whether JTT treatment longer than 6 months could induce a further increase in DAT and improve neuropsychological functions remains unknown.

To answer these questions, we designed this follow-up study as a time extension from our previous study (Liu et al. 2013). SPECT imaging with [^{99m}Tc]TRODAT-1 was used to assess DAT availability in detoxified heroin users and healthy controls. Heroin users were administered either JTT or placebo in a randomized, double-blind trial, and SPECT imaging was performed at four time points: a baseline scan after 15–18 days of detoxification, and three subsequent scans at 3, 6, and 12 months of treatment. Anxiety and depression ratings were also measured at the four time points to assess the

relationship between striatal DAT availability and neuropsychological functions.

Materials and methods

Subjects

Heroin users Sixty-four subjects (58 males and 6 females) with heroin dependence were recruited at the Drug Rehabilitation Center in Shanghai, China. 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 Twenty healthy subjects (15 males and 5 females) aged 18 to 55 years were recruited through newspaper advertisements and flier postings. The primary exclusion criterion was a past or present history of drug abuse, such as heroin, methamphetamine, MDMA, cannabis, and/or alcohol. Other exclusion criteria were the same as those for heroin users.

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

Study design

The study was a long-term, randomized, double-blind, placebo-controlled trial of JTT treatment for heroin abuse. The test medication was numbered with a completely randomized sequence that was generated by an independent third party using a protected computer database containing the randomization list. 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 they were given JTT (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 users were randomly assigned to treatment with either placebo or JTT in accordance with the order of drug numbering. The patients then received JTT or placebo from clinicians at oral doses of three tablets twice daily for the first 3 months, two tablets twice daily for the subsequent 3 months and one tablet twice daily for the last 6 months. 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 illicit drug use. The patients lived and conducted all other daily activities at the center, and they 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 blood and urine chemistries were analyzed at the four SPECT scanning time points.

SPECT imaging

SPECT imaging was performed as previously described with minor modifications (Kung et al. 1997). Each subject received 740 MBq (20 mCi) of the radiotracer [^{99m}Tc]TRODAT-1 (radiochemical purity >90 %) intravenously. Approximately 3 h after tracer injection, static SPECT brain imaging was performed using high-resolution fan beam collimators of a Siemens NME.CAM Gantry Dual Head Ex. Base (Siemens, Erlangen, Germany). SPECT 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 1995). The transverse image thickness was 4.0 mm (1 pixel). For each subject, the data were evaluated in the four consecutive transverse slices showing the highest tracer accumulation in the basal ganglia. Regions of interest (ROIs) were drawn manually on the subregions of both striatal and occipital areas using individual magnetic resonance imaging scans as a reference (non-registered) on SPECT scans by an experienced nuclear medicine physician, who was blinded to the group conditions and clinical information and had been previously trained and achieved high evaluation reliability (>0.95) (Yeh et al. 2012; Yuan et al. 2014). Magnetic resonance images from each subject were used as a guide for defining the striatum and occipital cortex (OC) in the SPECT images. The mean activity in the striatum was calculated by subtracting the mean counts per pixel in the OC as background from the mean counts per pixel in the bilateral striatum regions and dividing the result by the mean counts per pixel in the OC: (target−OC)/OC. For heroin users, imaging procedures were conducted at four time points: following the initial period of abstinence (baseline, post-detoxification, an average of 20 days from last heroin use) and at 3, 6, and 12 months of treatment. One SPECT imaging session was performed on healthy controls.

Neuropsychological evaluation

In heroin users, subjective depression and anxiety were assessed with the Hamilton Depression Rating Scale (HAMD) (Hamilton 1960) and the Hamilton Anxiety Rating Scale (HAMA) (Hamilton 1959) prior to each SPECT imaging session. The correlation between DAT levels in the bilateral striatum and HAMD or HAMA scores was determined at the four time points.

Statistical analysis

Differences in population characteristics among the groups were compared via the *t* test for continuous variables or the Chi-square test for categorical variables. Pearson product correlations were used to assess the relationship between DAT availability and the dose of heroin consumed, years of heroin use, and rating scale scores. Factorial analysis of variance (ANOVA) were applied to compare DAT availability between heroin-dependent subjects and healthy controls, with adjustment for the major baseline characteristics. Differences in DAT availability and rating scale scores between groups at the four time points were tested with the multivariate ANOVA, with the Bonferroni adjustment for multiple comparisons. DAT availability and rating scale scores at different times in each group were tested with repeated measures ANOVA. Post hoc analysis with Bonferroni adjustment was performed to assess the significance of the differences. Multivariable regression models were applied to compare DAT availability at different treatment times and different brain regions (right and left striatum) among the groups, with adjustments for baseline DAT availability. A linear mixed model analysis, with the subjects set as random effect, was used to evaluate the effects of JTT treatment on DAT availability and rating scale scores. The diagonal was constructed as the covariance structure. All tests were two-tailed, and significance was set at $p<0.05$. All statistics were performed using SPSS 17.0 software.

Results

Subjects

SPECT imaging was performed at baseline in 64 heroin users and 20 healthy subjects. Nine heroin users declined to participate in treatment after the baseline scan. Therefore, 55 heroin users were randomly assigned to treatment with either JTT or placebo. Three, four, and five subjects in the JTT treatment group, respectively, dropped out of the study after each of the subsequent SPECT imaging sessions. In the placebo group, three, two, and one subjects, respectively, also dropped out of the study after each of the subsequent SPECT imaging sessions. Ultimately, 37 heroin-dependent subjects (13 subjects in the JTT group and 24 subjects in the placebo group) completed all four SPECT scans in this study. The subject characteristics are presented in Table 1.

SPECT imaging analysis

Table 2 lists the results from the baseline scans. Compared with healthy controls, a significant reduction of DAT availability in heroin users was observed at baseline in the right striatum by 31.6 % (1.96±0.44 vs. 1.34±0.21, $p<0.001$) and in the left striatum by 33.2 % (1.93±0.34 vs. 1.29±0.17, $p<0.001$). These results suggest that chronic exposure to heroin results in a decreased availability of DAT.

Results from the four SPECT imaging sessions on two groups of heroin users are presented in Table 3. At baseline, no difference in DAT availability was found between the subjects placed into the placebo and JTT treatment groups. Over the next 12 months, DAT levels in the JTT-treated group increased steadily, and a significant time effect in the right striatum ($F=4.270$, $p=0.035$) and an obvious time effect in the left striatum ($F=3.709$, $p=0.050$) were observed. Post hoc *t* test indicated that DAT availability at 6 months of JTT treatment was significantly higher than that at baseline in the left striatum ($p=0.039$), and DAT availability at 12 months of JTT treatment was significantly higher than that at baseline in both the left ($p=0.004$) and right striatum ($p=0.003$). In the placebo group, there was also a significant time effect on DAT availability in both the right ($F=7.017$, $p=0.002$) and left striatum ($F=6.270$, $p=0.003$). Compared with baseline levels, DAT availability in the placebo group displayed a slight increase at 3 months, a slight decrease at 6 months and finally, a marked increase at 12 months. DAT availability at 12 months of placebo treatment was significantly higher than that at baseline or 3 and 6 months of treatment ($p<0.05$).

In the between-group comparison, DAT availability in the bilateral striatum was higher in the JTT-treated group than the placebo group after 3 and 6 months of treatment, and this difference reached significance at the 6-month time point ($p=0.004$). At the12-month time point, striatal DAT levels in both the placebo- and JTT-treated groups were similar and significantly higher than those at baseline. However, compared with the healthy control group, DAT availability in the left striatum of both placebo- and JTT-treated groups was still significantly lower ($p<0.05$), although in the right striatum the numerically lower value did not reach statistical significance compared with the healthy control group.

These results indicated that (1) downregulation of DAT in heroin users was long-lasting (for at least 6 months), (2) DAT levels remained lower than those in healthy controls, although they recovered notably after prolonged abstinence (for 12 months), and (3) JTT treatment accelerated the recovery of DAT.

Table 1 Demographic characteristics

	Heroin-dependent subjects			Healthy controls				
	All (n=37)	Jitai (n=13)	Placebo (n=24)	(n=20)				
		Mean (SD)		t (df=35)/Chi-square	p value[a]	Mean (SD)	t (df=35)/Chi-square	p value[b]
Male/female	33/4	13/0	20/4	3.721	0.054	15/5	1.881	0.170
Age (years)	36.4 (8.8)	34.5 (9.0)	37.5 (8.7)	0.017	0.323	32.3 (7.2)	0.744	0.081
BMI (kg/m^2)	20.8 (3.0)	20.8 (3.6)	20.8 (2.8)	1.124	0.099	22.8 (1.8)	6.306	0.007
Duration (years)	7.6 (3.5)	7.4 (3.87)	7.9 (3.2)	2.153	0.677			
Dose (g/day)	1.0 (0.5)	1.0 (0.6)	1.0 (0.5)	1.284	0.943			
Intake rout and no. (snorting/injection/both)	18/13/6	8/4/1	10/9/5	1.787	0.409			

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

Neuropsychological scores in heroin users at the four time points

Neuropsychological performance in heroin users was tested at baseline and at 3, 6, and 12 months. The results are shown in Table 4. Compared with the values measured at baseline, HAMA and HAMD scores decreased significantly at the 3-month time point in both the placebo- and JTT-treated groups (p<0.01), and continued to decrease thereafter. Compared with the 3-month time point, there was still a significant reduction of HAMA and HAMD scores at the 6-month time point in both groups (p<0.05); however, no significant changes were observed between the 6-month time point and the 12-month time point. Furthermore, no differences in either HAMA or HAMD scores between the two groups were observed in the four time points. These results indicated that heroin users experienced significant negative moods at the beginning of detoxification, as evidenced by the high HAMD and HAMA scores measured at baseline. However, moods improved fairly quickly upon abstinence.

Integration of DAT availability, heroin use and HAMA/HAMD scores

A significant negative correlation was observed between the average daily heroin dose and DAT level in the right striatum (r=−0.325, df=35, p=0.05). A significant negative correlation was also found between the years of heroin use and DAT levels in the left striatum (r=−0.386, df=35, p=0.018). In addition, significant positive correlations were also observed between the years of heroin use and HAMD scores (r=0.327, df=35, p=0.01), as well as between the average daily heroin dose and HAMA scores (r=0.484, df=35, p=0.002) (Fig. 1). However, no correlations were found between DAT levels and HAMA or HAMD scores at each time point (the figures with no significant correlation are not shown here). These results suggest that a longer duration and higher daily dose of heroin use may induce a more pronounced decrease in DAT availability and more severe anxiety or depression symptoms.

Table 2 Comparison of dopamine transporter (DAT) availability between heroin users (n=37) and healthy controls (n=20) at baseline

	DAT	Unadjusted			Adjusted[a]		
	Mean (SD)	β	SE	p	β	SE	p
Striatum (right)							
Healthy control	1.96 (0.44)	Ref			Ref		
Heroin-dependent subjects	1.34 (0.21)	−0.62	0.08	<0.001	−0.63	0.09	<0.001
Striatum (left)							
Healthy control	1.93 (0.34)	Ref			Ref		
Heroin-dependent subjects	1.29 (0.17)	−0.64	0.07	<0.001	−0.67	0.08	<0.001

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

Table 3 Measures of dopamine transporter (DAT) availability in placebo- and Jitai tablet-treated groups before treatment and after 3, 6, or 12 months of treatment

	DAT at baseline Mean (SD)	DAT at 3 months	DAT at 6 months	DAT at 12 months
Striatum (right)				
Placebo	1.34 (0.21)	1.36 (0.24)	1.26 (0.30)	1.67 (0.50)$^{\#}$
Jitai tablets	1.34 (0.21)	1.50 (0.28)	1.53 (0.28)*	1.64 (0.26)$^{\#}$
Striatum (left)				
Placebo	1.27 (0.15)	1.37 (0.23)	1.20 (0.33)	1.59 (0.41)$^{\#}$
Jitai tablets	1.33 (0.19)	1.46 (0.27)	1.53 (0.27)$^{*\#}$	1.52 (0.13)$^{\#}$

Adjustment for multiple comparisons: Bonferroni

*$p<0.01$ (significantly different from the placebo-treated group, with the adjustment for DAT in baseline); $^{\#}p<0.05$ (significantly different from the baseline)

Discussion

The purpose of the present follow-up study was to evaluate the time course of DAT changes in heroin users undergoing long-term abstinence and treatment with JTT. These results demonstrated that chronic heroin abuse resulted in impairment of the DA system, as evidenced by decreased DAT availability in the striatum. Moreover, this impairment was long-lasting, as shown by the persistently depressed DAT levels in the placebo group after 6 months of abstinence and the lower DAT levels in the left striatum in both the placebo- and JTT-treated groups after 12 months compared with the healthy controls. Treatment with JTT or prolonged abstinence induced a marked recovery of DA function, as evidenced by the increase in DAT availability in the subjects treated with JTT or placebo for 12 months compared with the baseline. However, the anxiety and depression symptoms induced by chronic heroin use improved greatly in the early stage of abstinence.

Chronic heroin use may lead to long-lasting neurotoxicity, which can be reversed by traditional Chinese medicine. In this one year study, the persistently low DAT availability was found even after 6 months of abstinence in the placebo group. This long-lasting reduction in DAT is consistent with findings from a previous imaging study (Shi et al. 2008), which reported lower DAT levels in heroin users compared with healthy controls after 6 months of abstinence. More importantly, our present double-blind, placebo-controlled trial found that treatment with TCM (JTT) could markedly increase the striatal DAT availability in heroin users. This result is consistent with a previous neuroimaging study, which found that U'finer™, another TCM, could also repair the damaged striatum over a 6-month treatment, although this work lacked an important placebo group for comparison (Jia et al. 2005). However, both of these previous studies stopped treatment and observation at the 6-month time period. Hence, questions remain as to whether longer treatment with JTT or abstinence would induce further recovery in DAT availability and neuropsychological performance in heroin users.

The present study, which extended the treatment and abstinence period to 12 months, found a long-lasting impairment in the striatum. Although the DAT levels recovered dramatically with prolonged abstinence or JTT treatment for 1 year, they still remained significantly lower in the left striatum than those in the healthy controls. This long-lasting reduction in DAT availability was observed previously by Yeh et al., who found lower striatal DAT availability in 12 heroin users even after a mean of 488 days in abstinence (Yeh et al. 2012). This suggests that the heroin-induced impairment in striatal dopaminergic neurons is partially but not completely reversible either by treatment with JTT or long-term abstinence.

The time period for the recovery of striatal DAT availability in users of drugs upon abstinence differed across the various drugs of abuse. For example, DAT was shown to return to normal levels after 3 months of abstinence in cocaine users (Beveridge et al. 2009) and upon acute withdrawal in alcoholics (Bustamante et al. 2014). However, DAT reduction induced by chronic methamphetamine addiction was long lasting, and recovery took prolonged (9 months) abstinence (Volkow et al. 2001b). Our current study, as well as that of Yeh et al. (2012), demonstrated that the time course for the

Table 4 Scores of subjective anxiety and depression in heroin users at different time points

	Baseline Mean (SD)	3 months	6 months	12 months
Anxiety				
Placebo	13.30 (7.45)	4.74 (4.90)$^{\#}$	2.17 (3.43)$^{\#*}$	3.43 (3.49)$^{\#}$
Jitai tablets	10.83 (6.16)	3.83 (3.21)$^{\#}$	1.75 (2.73)$^{\#*}$	2.00 (1.91)$^{\#}$
Depression				
Placebo	11.91 (6.04)	5.04 (3.71)$^{\#}$	2.30 (3.78)$^{\#*}$	3.83 (4.26)$^{\#}$
Jitai tablets	9.08 (4.85)	5.08 (2.91)$^{\#}$	1.75 (2.45)$^{\#*}$	1.42 (2.15)$^{\#}$

Adjustment for multiple comparisons: Bonferroni

*$p<0.05$ (anxiety/depression scores, significantly different from the 3 months); $^{\#}p<0.05$ (anxiety/depression scores, significantly different from the baseline)

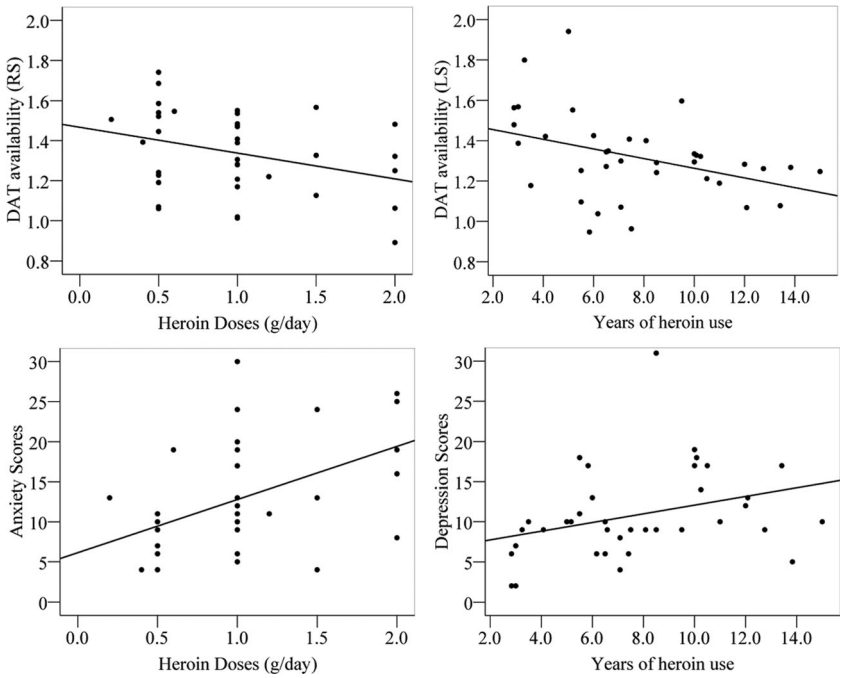

Fig. 1 Scatter plots showing that at baseline, the heroin doses were significantly associated with the DAT availability in the right striatum (*RS*; $r=-0.325$, $df=35$, $p=0.05$) and anxiety scores ($r=0.484$, $df=35$, $p=0.002$) and the years of heroin use were also significantly correlated with the DAT availability in the left striatum (*LS*; $r=-0.386$, $df=35$, $p=0.018$) and the depression scores ($r=0.327$, $df=35$, $p=0.01$)

recovery of DAT impairment induced by chronic heroin use appeared to be similar to that of methamphetamine, and a complete return to normal levels was still not observed even after abstinence of 12 months or longer. Long-term decreases in DAT have been shown to be associated with drug cravings, which in turn can lead to drug-seeking behavior and a relapse in abstinent individuals with history of drug abuse (Hartz et al. 2001; Yuan et al. 2014). Therefore, treatment strategies aimed at normalizing striatal DAT may be valid and effective for the prevention of relapse in drug addiction and treatment.

JTT has been approved for the treatment of opioid dependence with no addictive composition. Previous clinical trials have documented that JTT is efficacious at controlling and relieving withdrawal symptoms with no dependence potential and no obvious adverse side effects (Xiong et al. 2002; Xu et al. 2000). Long-term treatment with JTT combined with psychological intervention and social support has been shown to be effective at promoting retention and preventing relapse in community-based heroin addiction treatment and adverse events from the drug are rare (Hao et al. 2013). In the present study, we demonstrated that JTT treatment effectively increased DAT availability in heroin users. DAT availability in the bilateral striatum after 6 months in the JTT-treated group was significantly higher than that in the placebo group. After 12 months of treatment with JTT, DAT levels almost recovered to normal levels in the right striatum of heroin users. Prior studies in human and animals have reported that some herbs and components in the JTT formula were effective at regulating DA function (Kin et al. 1995; Liu et al. 2014; Tsukada et al. 2000; Yang et al. 2008). For example, scopolamine, a muscarinic cholinergic antagonist, modulates DA turnover in the striatum by simultaneous enhancement on the dynamics of DA synthesis and DAT availability through the inhibition of muscarinic cholinergic neuronal activity (Tsukada et al. 2000). *L*-THP, a DA antagonist, significantly ameliorates withdrawal syndrome and increases the abstinence rate among heroin users (Yang et al. 2008). The underlying mechanism of *L*-THP may involve increases in the synthesis and release of endogenous opioid peptides (Chu et al. 2008). Ginseng was previously reported to be effective at inhibiting the behavioral effects of drugs by possibly modulating the central dopaminergic system (Lee et al. 2008, 2011). Clear mechanism(s) of action can hardly be attributed to a prescription constituted of a complex herbal mixture (with 15 different herbs and at least 101 compounds identified in a previous study) (Wang et al. 2012). Although recovery of DAT and normalization of neuropsychological performance have been conspicuously demonstrated in the present study, it remains difficult to pinpoint how, and which of the putative active compounds or components effectively modulates the striatal DA function. The underlying mechanism of JTT's ability to upregulate DAT levels in heroin users may derive from the combined effects of these active ingredients, as well as others. However, its exact nature remains to be elucidated.

Chronic drug abuse induces anxiety and depression symptoms, which play a role in impulsive drug-seeking behavior and relapse (Gerra et al. 2000; Hartz et al. 2001). We found that the time course of anxiety and depression remission in the JTT-treated group was synchronous with the placebo group, which recovered significantly at the early stage of treatment with JTT or placebo. However, this recovery process did not coincide with that of DAT availability, which recovered very

slowly, as evidenced by the significant increase in DAT availability after at least 6 months or longer period of treatment. Similar discordance between DAT levels and psychiatric ratings was also observed in another study (Shi et al. 2008), which found a significant difference in DAT levels but no difference in subjective anxiety scores between subjects in prolonged abstinence and methadone maintenance treatment. Moreover, we found no correlation between DAT availability and HAMA or HAMD scores in the bilateral striatum. This suggests that the negative moods in heroin users may dissipate fairly quickly upon abstinence or treatment with JTT. However, the recovery of DA function appeared to take longer. This could occur if the negative mood induced by heroin use was also regulated by other systems that may have been affected by heroin for which recovery is rapid. Withdrawal-induced depressive-like behavior has been reported to be associated with specific changes in serotonergic neurotransmission and the HPA axis, as well as alterations in hippocampal neuroplasticity (Renoir et al. 2012). Evidence also suggests that the serotonergic and stress systems contribute to the negative affective states associated with abstinence from the drug in question (Watkins et al. 2000). Moreover, previous studies that evaluate mood changes (depression and anxiety) primarily focus on the first month of abstinence or treatment (Adams et al. 1995; Goeldner et al. 2011; Li et al. 2009; Shi et al. 2009). Therefore, this discordance between the changes in DAT levels and psychiatric ratings was valid and helpful for the understanding of the neuropsychiatric regulation system in opioid addiction.

It was noted that the mean values of DAT availability in the left striatum of both healthy controls and heroin subjects were lower than those in the right striatum; however, no statistical significance was observed. This right-greater-than-left asymmetry has been reported in previous studies where healthy people were found to have the right-greater-than-left asymmetry in D_2 receptor and DAT availability in the caudate (Laakso et al. 2001; Tomer et al. 2008). Moreover, several imaging studies in opioid or methamphetamine dependent subjects and healthy controls also found a slight right-great-than-left asymmetry in DAT levels in the striatum (Liang et al. 2014; Liu et al. 2013; Shi et al. 2008; Yuan et al. 2014). Nevertheless, no significant differences in these right-greater-than-left asymmetries were reported. Therefore, this asymmetry may result from the functional or structural differences of the bilateral brain.

Our findings demonstrated an association between a low level of DAT availability and greater amount of heroin use. This is in agreement with the findings of a recent study by Lin et al., which showed an obvious negative correlation between striatal DAT availability and annual expenditure on heroin that may reflect the cumulative amount of heroin use in 1 year (Lin et al. 2015). The prolonged use of heroin results in a downward regulation in dopaminergic activity, which plays a critical role in drug craving, drug-seeking, and relapse. Therefore, such a finding may also suggest that subjects with lower DAT levels use more heroin. However, a recent imaging study reported no association between DAT availability and the quantity of heroin use per day (Cosgrove et al. 2010). The major reason that led to the discrepancies among these studies may be the sample size: 37 and 21 subjects were included in our study and that of Lin et al. (2015), respectively, while a smaller sample size of 8 subjects was used in the study of Cosgrove et al. (2010), which may have limited their statistical power to detect the association between DAT availability and heroin use characteristics.

Some of the limitations of this study should be noted. Firstly, this study lacked the evaluation on heroin craving. As craving is one of the most characteristic experiences in addiction, and can be regarded as an important mediator of continued substance use and relapse after abstinence (Sayette et al. 2000), further studies with craving evaluation are necessary. Secondly, a potentially confounding influence of age may exist on DAT availability comparisons between heroin users and healthy controls. The heroin users were somewhat (although not significantly) older than healthy controls. Although age-related reductions in the DAT are known to occur (Volkow et al. 1994), the reported age-related decreases are not of the degree observed in the present study. However, in the present study, we found no correlation between age and DAT availability in the bilateral striatum of heroin users. Meanwhile, the regression model was adjusted for age. Thirdly, the smoking status of participants in the present study was unavailable. Usually, nicotine dependence is much more prevalent among heroin users than in the general population (Kabir et al. 2013); thus, examining the smoking status of the participants would be important. Finally, higher DAT availability in women than in men has been previously reported (Varrone et al. 2013). As male heroin users outnumbered females in the rehabilitation center, a gender bias was obvious in the present study. However, the difference of gender among the three groups in our study did not reach a significance. Moreover, the DAT availability comparison between heroin-dependent subjects and healthy controls or between the JTT treatment group and placebo group has been adjusted for gender effect.

Conclusion

This is the first investigation into the time course of both DAT recovery and negative mood changes in chronic heroin users undergoing treatment with JTT or abstinence for 12 months. In this study, we provided further evidence that heroin abuse induces a significant decrease in striatal DAT, and that DAT recovers upon treatment with the TMC formulation JTT for at least 3 months, and following long-term abstinence of

12 months. We also showed that the negative moods in heroin users improve fairly quickly, and the recovery of neuropsychological function does not parallel the recovery in striatal DAT levels, as evidenced by decreases in depression and anxiety scores preceding the increase in DAT levels.

In summary, in this follow-up study, we further demonstrated that treatment with JTT accelerates the recovery of both DAT levels and moods during long-term abstinence, thus affirming and extending the findings from our previous study on the effectiveness of JTT in promoting DAT recovery in heroin users. Note that the present study also revealed that, despite the significant recovery of DAT levels in heroin users after 12 months of JTT treatment or abstinence, a complete return to normal levels was not observed, which underscores the long-lasting nature of heroin-induced DA function deficits. Future studies may explore whether treatment with JTT longer than 12 months can completely reverse heroin-induced DAT impairment and prevent relapse.

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

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