Abstract—Replacement therapy with buprenorphine is clinically effective in reducing withdrawal and craving for heroin during detoxification but not in decreasing the probability of relapse after detoxification. This study examined the acute effects of buprenorphine on brain responses to heroin-related cues to reveal the neurobiological and therapeutic mechanisms of addiction and relapse. Fifteen heroin addicts at a very early period of abstinence, were studied in two separate periods 10–15 min apart: an early period (5–45 min) and a later period (60–105 min) after sublingual buprenorphine, roughly covering the onset and peak of buprenorphine plasma level. During both periods, fMRI scanning with heroin-related visual stimuli were performed followed by questionnaires. Under effect of buprenorphine, brain responses to heroin-related cues showed decrease in amygdala, hippocampus, ventral tegmental area (VTA) and thalamus but no changes in ventral striatum and orbital–prefrontal–parietal cortices. As an uncontrolled trial, these preliminary results suggest that buprenorphine has specific brain targets in reducing withdrawal and craving during early abstinence, and that ventral striatum and orbital–prefrontal–parietal cortices may be the key targets in developing therapy for drug addiction and relapse. © 2010 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: heroin, addiction, buprenorphine, relapse, fMRI, replacement therapy.

In the past two decades, the development of new research technology has greatly advanced our understanding of the neurobiological mechanisms and therapeutic strategies for drug addiction. Many chemical medications have been produced, some of which have been widely used in clinical treatment of drug addiction (Kreek et al., 2002), such as methadone and buprenorphine for heroin replacement therapy (O’Brien, 2005), and naltrexone for heroin and alcohol anticraving treatment (Dackis and O’Brien, 2005; O’Brien, 2005). These medications, however, have been found unable to prevent drug relapse following detoxification on a long-term basis (Heidbreder and Hagan, 2005; O’Brien, 2005). For example, naltrexone suppresses euphoria from heroin via its antagonistic effect on opiate receptors, but most heroin addicts would not accept it for long-term therapy (O’Brien, 2005). Methadone and buprenorphine, as opiate agonists, are clinically effective in reducing withdrawal and craving for heroin during detoxification, but it is difficult to use them to reduce the likelihood of relapse after detoxification (O’Brien, 2005). As these results are well-known and seem very robust, it is a crucial research question to understand why methadone or buprenorphine fails to reduce the probability of relapse. Such understanding would help revealing the neurobiological mechanisms of relapse and designing better therapeutic strategies.

One way to address this question is using fMRI to study the dynamic interaction between brain circuitry and neuropsychopharmacological agents. There are so many advantages to the method that it has already formed a field of its own called pharmacological MRI (phMRI) in the past decade (Leslie and James, 2000; Tracey, 2001; Honey and Bullmore, 2004). PhMRI is considered to offer a good way to assess pharmacological effects of medications for addiction therapy such as methadone or buprenorphine, and to understand the neurobiological mechanism of relapse after detoxification (Dackis and O’Brien, 2005).

Recently, Langleben et al. (2008) first employed phMRI to investigate acute effects of methadone on brain responses to heroin-related cues. Heightened responses to heroin-related stimuli were found acutely reduced after methadone administration in insula, amygdala, and hippocampus, but not in orbitofrontal and ventral anterior cingulate cortex. The findings led the authors to conclude that the medial prefrontal cortex and the extended limbic system in methadone maintenance addicts with a history of heroin dependence remain responsive to salient drug cues, suggesting a continued vulnerability to relapse.

With the increasing use of buprenorphine in the treatment of opiate dependence, it is necessary to further study the neuropsychopharmacological mechanism of buprenorphine and to find an objective evaluation of its curative effects. As buprenorphine binds with high affinity to both the μ opiate receptors (as a partial agonist) and the κ

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opiate receptors (as an antagonist), it combines the pharmacological benefits of full opiate agonists like methadone and antagonists like naltrexone to block effects of illicit opiates and deter their abuse (Woody et al., 2008). Further, because buprenorphine causes little euphoria and is less likely to be abused, it is much safer than full agonists such as methadone and has a greater degree of treatment ease and compliance than naltrexone (Collins and McAllister, 2007). Previous studies have demonstrated that the effectiveness of buprenorphine for treatment of opiate dependence is comparable to methadone in reducing withdrawal and craving in detoxification (Ling and Wesson, 2003; Oreskovich et al., 2005; Leonardi et al., 2008).

In the present study, we used phMRI to examine acute effects of sublingual buprenorphine on brain responses to heroin-related cues at a very early period of heroin abstinence. Such preliminary data would identify brain regions in which neural responses to heroin-related cues are affected by buprenorphine as its therapeutic targets. Meanwhile, the unaffected brain regions may help to understand its limited therapeutic effects on addiction. Additionally, comparison between the effects of buprenorphine and methadone observed in the literature should help to reveal commonalities and differences in their brain mechanisms in addiction therapy and to provide further evidence for the application of phMRI in therapeutic research on drug addiction.

**EXPERIMENTAL PROCEDURES**

**Participants**

Fifteen active heroin users (mean age = 33.5 years, SD = 7.9, one female) all meeting DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) criteria for current (at least prior 6 months) dependence on heroin participated in this study. All had normal vision and were strongly right-handed. They were native inpatients from a detoxification clinic in the local city (Shantou, PR China). Heroin was the primary drug of choice for all participants (six by sniffing or smoking, nine by injecting). Participants’ average heroin use history was 4.5 years (SD = 4.4) with a mean dose of 2.5 g (SD = 2.4) per day. For all participants, the length of prior-study abstinence was longer than 12 h (mean = 50 h, SD = 24), a period inducing moderate heroin craving, based on interviews with addict participants in a previous study (Xiao et al., 2006). Their participation in this study was from 12 to 36 h after they entered the detoxification clinic. All participants were current tobacco users (mean = 28 cigarettes per day, SD = 12) and only one reported habitual alcohol use. There was no other drug abuse for them. None had any neurological or psychiatric disorders other than substance dependence.

Observing the Declaration of Helsinki, written informed consent was obtained from each participant following a research protocol approved by the Human Subjects Review Committee of the Medical College of Shantou University. All participants were clearly informed that they were free to participate and to terminate throughout the study without incurring any punishment.

**Buprenorphine**

Sublingual tablets of buprenorphine (2.0 mg per tablet, Qinghai Pharmaceutical Factory, Qinghai, PR China) were used in this study and were provided by the detoxification clinic. Experimentally and empirically, concentration of buprenorphine in blood peaks around 1–1.5 h following sublingual administration (Mendelson et al., 1999; Strain et al., 2004; Chawarski et al., 2005; Ciraulo et al., 2006), with a plasma half-life of about 3 h (Gutstein and Akil, 2006).

**Design and procedure**

The time of study was held constant for all participants at 13:00 to 15:00 ev. Their participation in this study was either prior to their receiving any clinical treatment or more than 8 h after receiving their first single dose buprenorphine (2.0 or 4.0 mg) in the detoxification clinic. Following a sublingual administration of buprenorphine (2.0 or 4.0 mg), participants were scanned in two periods, an early period from 5 to 45 min, and a late period from 60 to 105 min, each for about 35–40 min long. The two periods were selected to capture the onset and peak, respectively, of sublingual buprenorphine plasma levels (Mendelson et al., 1999; Strain et al., 2004; Chawarski et al., 2005; Ciraulo et al., 2006). Pharmacologically and therapeutically, the effect of buprenorphine in the late period should be greater than in the early period.

In between the two scans, participants were removed from the scanner and took a short break (10–15 min), during which they completed a questionnaire. They completed the same questionnaire again after the second scan was ended. Other than buprenorphine, no use of tea, caffeine, cigarette, alcohol, and other drug and medicine was allowed 8 h prior to the study and during the study.

Within each scan period, each participant underwent three functional runs and two structural runs, with a 2–3 min interval between two neighboring runs. In each run, there were three blocks presenting heroin-related images and three blocks presenting neutral images, in alternative order and separated by a 26 s fixation as the resting baseline. In each block, four images were presented, each for 5 s with zero inter-stimulus interval, followed by a 4 s interval during which participants were instructed to press a button once to indicate they were attentive in passively viewing the images. The total length for each run was 5 min 38 s.

The heroin-related stimuli were taken from our previous study (Xiao et al., 2006) consisting of 24 heroin-related images of heroin drugs, drug injection, smoking or preparation scenes, and 24 graphically and contextually matched neutral images of flowers, toys, furniture, everyday activities (e.g., reading or playing sport), or street scenes. Stimuli were presented using the Inquisit software package (Psychology Software Tools, Pittsburgh, PA, USA).

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**Subjective heroin craving was assessed on a 10-point (0 to 9) scale (Langleben et al., 2008; 0 for least craving and 9 for strongest craving) before and after buprenorphine administration, and after both the early and the late scans. After each scan, participants also evaluated their response to the images they just saw by completing retrospective self-report measures consisting of 10 questions adapted from Garavan et al. (2000).**

**Image acquisition**

Participants lay supine inside the scanner and wore goggles specially designed for MR environment. They were told to keep their head still inside the scanner.

All MR imaging was conducted at the Medical College of Shantou University on a 1.5 T Philips MR scanner with a standard headcoil. Twenty axial slices covering the whole brain were acquired with a T2*-weighted gradient-echo echo planar imaging pulse sequence (GE-EPI, TR = 2000 ms, TE = 45 ms, flip angle = 90 degrees, matrix = 64×64, FOV = 230×230 mm2, slice thickness = 6 mm, gap = 0 mm) for blood-oxygen-level-dependent (BOLD) functional imaging. This sequence delivered a voxel res-
olition of 3.59±3.59±6 mm³ for the functional data. Coplanar images were acquired with a T1-weighted spin echo pulse sequence (SE, TR=509 ms, TE=14 ms, matrix=256×256), along with a high-resolution 3-D image using spoiled gradient recalled echo pulse sequence (SPGR, 120 slices, TR=30 ms, TE=3.0 ms, flip angle=30 degrees, matrix=256×256, FOV=230×230 mm², slice thickness=1.3 mm, gap=0 mm). The same imaging parameters were used for the two scans, each with acquisition of the structural and the functional images.

Imaging data analysis

Image analysis was carried out with SPM2 software (Wellcome Department of Cognitive Neurology, London, UK). Functional images were motion corrected, normalized to the SPM EPI template, interpolated to 4 mm isotropic voxels, spatially smoothed (Gaussian filter of 8 mm kernel). High-pass temporal filtering and scaling using mean-based intensity normalization were then performed on the images (Langleben et al., 2008) before they were entered into a regression analysis using the general linear model for block designs in SPM. Participants with excessive head motion (more than 1 voxel in translation or 2 degrees in rotation) would be excluded from the regression analysis (Bertolino et al., 2004).

Regressors were constructed for the two types of blocks (heroin-related vs. neutral), with each block modeled with a square-waved epoch, convolved with the canonical hemodynamic response function in SPM. Following the regression analysis, three linear contrasts were constructed for each participant, that is, heroin-related vs. rest, neutral vs. rest, and heroin-related vs. neutral. The resulting subject-specific parameter estimates for these contrasts, computed separately for the early period and the later period, were then entered into a standard second-level whole brain analysis in SPM with one-sample t-tests.

The critical contrast of interest was the heroin-related vs. neutral contrast that would reveal brain activations related to processing of heroin-related cues (Langleben et al., 2008), which would be referred to next as the “heroin-related cues” contrast for simplicity. We directly compared the two scans, using voxel-wise random effects paired t-tests (Langleben et al., 2008) to identify regions in which brain activation to heroin-related cues was different across the two scans.

These regions were then subject to post-hoc region of interest (ROI) analysis (using Marsbar 0.41, http://marsbar.sourceforge.net) to see their specific pattern of brain responses to the heroin-related images and the neutral images in both the early and the late scans (Bertolino et al., 2004). Additionally, in the above ROIs, we analyzed the correlations between changes of magnitude of brain activations to heroin-related cues from the early to the late period with participants’ heroin use history. Statistical significance was set at P<0.005 based on t-tests with a critical t-value of 3.11 (df=11) and cluster size threshold was set at a minimum of 10 voxels in all whole brain analysis. All coordinates reported were in the MNI space.

### RESULTS

#### Behavioral results

Three of the 15 participants were excluded from the imaging analysis due to excessive head motion. As the button task was designed to ensure task engagement, this part of the behavioral data were only analyzed for the remaining 12 participants to be consistent with the imaging analysis. The subjective rating data were valid for all 15 participants.

For the button press task, response rates were comparable between the early and the late periods (mean±SD, 83.6±30.5% vs. 86.1±26.5%, t=0.85, df=11, P>0.1). There was no difference of response rates to heroin-related images between the early and late scan (mean±SD, 82.9±32.6% vs. 86.1±23.3%, t=0.79, df=11, P>0.1), and no difference to neutral images (mean±SD, 84.3±29.8% vs. 86.1±30.4%, t=0.79, df=11, P>0.5). The response rates between heroin-related images and neutral images were not different in the early scan (t=0.71, df=11, P>0.1), nor were in the late scan (t=0, df=11, P=1). The repeated-measures ANOVA did not reveal any significant effect for stimulus type, scan period, and their interaction (all Fs<1, all Ps>0.1).

Subjective heroin craving was assessed at five time points. Craving scores were 3.7 (SD=3.9) before buprenorphine administration, and 2.4 (SD=2.8) 5 min after the administration and just before the early scan. The scores were 1.9 (SD=2.9) right after the early scan, 2.3 (SD=2.7) just before the late scan, and 1.6 (SD=2.9) right after the late scan. The value before administration was significantly higher than that 5 min after administration (t=2.54, df=14, P<0.05). The four values after administration did not differ from each other significantly in a one-way ANOVA test (F=0.23, P=0.5).

Out of the 10 self-report questions, there were four showing significant effects of image type or early vs. late scan (Table 1).

#### Imaging results

**Whole brain analysis.** For the early scan, there was significant brain activation to heroin-related cues in left VTA (ventral tegmental area), thalamus, hippocampus, OFC (orbitofrontal cortex), ventral caudate/NAc (nucleus accumbens), superior occipital gyrus and precentral gyrus, right postcentral gyrus, inferior temporal gyrus and lingual

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### Table 1. Mean scores (±SD) of self-report ratings on four questions about test images across the two scan periods

<table>
<thead>
<tr>
<th>Question</th>
<th>Scan 1 (early period)</th>
<th>Scan 2 (late period)</th>
<th>Comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D1</td>
<td>N1</td>
<td>D2</td>
</tr>
<tr>
<td>1</td>
<td>2.27±2.05</td>
<td>0.64±1.50</td>
<td>1.27±1.68</td>
</tr>
<tr>
<td>2</td>
<td>1.73±2.41</td>
<td>0.91±1.58</td>
<td>1.0±1.67</td>
</tr>
<tr>
<td>3</td>
<td>1.60±2.30</td>
<td>3.90±2.90</td>
<td>1.00±1.10</td>
</tr>
<tr>
<td>4</td>
<td>0.91±2.12</td>
<td>3.45±3.14</td>
<td>0.64±1.02</td>
</tr>
</tbody>
</table>

Question: (1) “When watching these images, how much did you want to use heroin?” (2) “When watching these images, how much did they excite you?” (3) “When watching these images, how much did you like them?” (4) “How much did you want to see more of these images?”

D represents ratings on heroin-related images, N represents ratings on neutral images, D1 and N1 for scan 1, D2 and N2 for scan 2. P-values are based on two-tailed t-tests (df=14) except the one marked with * which is a one-tailed t-test.
gyrus, bilateral amygdala, superior parietal lobule and inferior frontal gyrus (Fig. 1A, Table 2).

For the late scan, there was significant brain activation to heroin-related cues in left postcentral gyrus, supramarginal gyrus, superior parietal lobule and middle occipital gyrus, right OFC, inferior temporal gyrus and inferior parietal lobule, bilateral inferior frontal gyrus. Unlike in the early scan, there was no activation in VTA, thalamus, amygdala, hippocampus and ventral caudate/NAc in the late scan (Fig. 1B, Table 2).

Direct comparison between the two scans showed that brain activation to heroin-related cues was significantly greater for the early scan in left VTA, thalamus, paracentral lobule, middle temporal gyrus and calcarine

Table 2. Brain activation from voxel-based whole brain analysis in the two scan periods

<table>
<thead>
<tr>
<th>Early scan period</th>
<th>Coordinates</th>
<th>t max</th>
<th>Volume*</th>
<th>Late scan period</th>
<th>Coordinates</th>
<th>t max</th>
<th>Volume*</th>
</tr>
</thead>
<tbody>
<tr>
<td>L superior parietal lobule</td>
<td>−32, −56, 56</td>
<td>9.02</td>
<td>231</td>
<td>L superior parietal lobule</td>
<td>−56, −28, 32</td>
<td>7.76</td>
<td>60</td>
</tr>
<tr>
<td>R superior parietal lobule</td>
<td>−28, −64, 56</td>
<td>8.90</td>
<td>109</td>
<td>R inferior parietal lobule</td>
<td>−28, −52, 52</td>
<td>6.62</td>
<td>69</td>
</tr>
<tr>
<td>R postcentral gyrus</td>
<td>−40, −44, 64</td>
<td>5.02</td>
<td></td>
<td>R orbitofrontal cortex</td>
<td>−52, 36, −4</td>
<td>6.33</td>
<td>24</td>
</tr>
<tr>
<td>R inferior frontal gyrus</td>
<td>−60, 20, 24</td>
<td>8.11</td>
<td>74</td>
<td>R middle occipital gyrus</td>
<td>−44, −80, 0</td>
<td>6.06</td>
<td>101</td>
</tr>
<tr>
<td>R inferior temporal gyrus</td>
<td>−52, −72, −8</td>
<td>7.70</td>
<td>174</td>
<td>L superior parietal lobule</td>
<td>−24, −56, 64</td>
<td>6.08</td>
<td>63</td>
</tr>
<tr>
<td>L ventral caudate/NAc</td>
<td>−8, 12, 0</td>
<td>6.97</td>
<td>12</td>
<td>L inferior parietal lobule</td>
<td>−52, 36, 8</td>
<td>5.80</td>
<td>18</td>
</tr>
<tr>
<td>L orbitofrontal cortex</td>
<td>−44, 20, −16</td>
<td>6.26</td>
<td>12</td>
<td>L inferior frontal gyrus</td>
<td>−56, 16, 20</td>
<td>5.02</td>
<td>77</td>
</tr>
<tr>
<td>L amygdala</td>
<td>−40, 36, −4</td>
<td>4.14</td>
<td>31</td>
<td>R inferior temporal gyrus</td>
<td>−52, −72, −8</td>
<td>5.71</td>
<td>93</td>
</tr>
<tr>
<td>L inferior frontal gyrus</td>
<td>−52, 40, 12</td>
<td>5.15</td>
<td>31</td>
<td>R inferior frontal gyrus</td>
<td>−52, 8, 24</td>
<td>5.27</td>
<td>61</td>
</tr>
<tr>
<td>L precentral gyrus</td>
<td>−52, 16, 24</td>
<td>5.83</td>
<td>31</td>
<td>L postcentral gyrus</td>
<td>−40, −36, 48</td>
<td>4.61</td>
<td>19</td>
</tr>
<tr>
<td>L thalamus</td>
<td>0, −12, 0</td>
<td>6.12</td>
<td></td>
<td>R lingual gyrus</td>
<td>36, −88, 20</td>
<td>4.35</td>
<td>21</td>
</tr>
<tr>
<td>L VTA</td>
<td>0, −16, −8</td>
<td>3.78</td>
<td>35</td>
<td>R amygdala</td>
<td>24, 0, −20</td>
<td>4.90</td>
<td>12</td>
</tr>
<tr>
<td>R amygdala</td>
<td>24, 0, −20</td>
<td>4.90</td>
<td>12</td>
<td>L superior occipital gyrus</td>
<td>−24, −88, 36</td>
<td>4.60</td>
<td>16</td>
</tr>
<tr>
<td>R hippocampus</td>
<td>−16, −8, −16</td>
<td>3.97</td>
<td></td>
<td>L amygdala</td>
<td>−24, 0, −20</td>
<td>4.51</td>
<td>26</td>
</tr>
<tr>
<td>R lingual gyrus</td>
<td>36, −88, 20</td>
<td>4.25</td>
<td></td>
<td>R lingual gyrus</td>
<td>36, −88, 20</td>
<td>4.25</td>
<td>21</td>
</tr>
</tbody>
</table>

(x, y, z) for center of mass in MNI space. All statistical thresholds set at \(P < 0.005\) based on one-sample \(t\)-tests with a critical \(t\) value of 3.11, \(df = 11\). Cluster size threshold set at a minimum of 10 voxels.

* Volumes given as number of active voxels, voxel size \(4 \times 4 \times 4\) mm\(^3\). R, right; L, left; VTA, ventral tegmental area; NAc, nucleus accumbens.
sulcus, right amygdala, hippocampus, precentral gyrus and postcentral gyrus, compared to the late scan. No brain region showed significantly greater activation to heroin-related cues for the late scan compared to the early scan (Fig. 1C, Table 3).

**ROI analysis.** Brain regions showing differential brain activation to heroin-related cues across the two scans were set as the functional ROIs and analyzed further as follows. The averaged BOLD percent signal changes in each ROI were calculated for each participant in four conditions and then submitted to a $2 \times 2$ repeated-measures ANOVA (using SPSS 13.0 for Windows; SPSS Inc., Chicago, IL, USA) with image type (heroin-related vs. neutral) and scan order (early vs. late) as the two factors. In all ROIs, the analysis did not show any main effects but a significant image type by scan order interaction effect ($P < 0.05$), and the signals decreased for the heroin-related stimuli from the early to the late scan, but increased for the neutral stimuli. In Fig. 2, the patterns of signal changes to different stimuli in left VTA and thalamus, right amygdala and hippocampus are illustrated. In other ROIs, including left paracentral lobule, middle temporal gyrus and calcarine sulcus, right precentral gyrus and postcentral gyrus, the patterns were similar.

<table>
<thead>
<tr>
<th>Brain regions</th>
<th>Coordinates</th>
<th>$t_{\text{max}}$</th>
<th>Volume*</th>
</tr>
</thead>
<tbody>
<tr>
<td>L middle temporal gyrus</td>
<td>−48, −64, 20</td>
<td>5.76</td>
<td>22</td>
</tr>
<tr>
<td>L calcarine sulcus</td>
<td>−8, −68, 12</td>
<td>5.63</td>
<td>16</td>
</tr>
<tr>
<td>R precentral gyrus</td>
<td>32, −16, 56</td>
<td>5.38</td>
<td>22</td>
</tr>
<tr>
<td>R postcentral gyrus</td>
<td>24, −28, 60</td>
<td>4.04</td>
<td></td>
</tr>
<tr>
<td>R amygdala</td>
<td>20, 0, −12</td>
<td>5.10</td>
<td>15</td>
</tr>
<tr>
<td>R hippocampus</td>
<td>32, −8, −12</td>
<td>3.60</td>
<td></td>
</tr>
<tr>
<td>L paracentral lobule</td>
<td>−4, −24, 56</td>
<td>4.43</td>
<td>15</td>
</tr>
<tr>
<td>L VTA</td>
<td>0, −12, −12</td>
<td>3.59</td>
<td>22</td>
</tr>
<tr>
<td>L thalamus</td>
<td>−12, −20, 4</td>
<td>3.46</td>
<td></td>
</tr>
<tr>
<td></td>
<td>−4, −12, 0</td>
<td>3.14</td>
<td></td>
</tr>
</tbody>
</table>

Statistical significance set at $P < 0.005$ based on paired t-tests with a critical $t$-value of 3.11 ($df = 11$). Cluster threshold set at a minimum of 10 voxels.

* Volumes are given as number of active voxels, the voxel size is $4 \times 4 \times 4$ mm$^3$. R, right; L, left; VTA, ventral tegmental area.

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**Fig. 2.** BOLD signal changes to heroin-related and neutral stimuli across the two scans revealed from the ROI Analysis. D represents signal changes to heroin-related images, N represents signal changes to neutral images. Error bars represent SEM. VTA for ventral tegmental area. For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.
In the above ROIs, the associations between signal changes in brain activation to heroin-related cues from the early to the late period and participants' heroin use history were analyzed (with Pearson’s correlation in SPSS 13.0). No association was found in any of the ROIs (all $P > 0.1$).

**DISCUSSION**

The response rates of button press task were approximately 80% in both scans of the study, and there were no differences between the two scans and the two types of stimuli. Missed responses were randomly distributed in each run and did not show any regular pattern. They were mostly due to pressing the button too lightly or pressing the wrong button, based on participants’ report. Some were unskilled in responding while wearing goggles. There was no sign that participants were not attending to the stimuli.

In this study, the craving score showed a significant decline only 5 min after buprenorphine administration, before the drug could have any physiological effects. However, the scores stayed at the same level throughout the remaining time when brain activations to heroin-related cues showed significant changes. This indicates that the addicts were highly suggestive to the effects of buprenorphine, and demonstrated the usefulness of fMRI to provide objective measures (Dackis and O'Brien, 2005) beyond subjective self-report.

Different from rating scores, stimulus rating reflected the effects of buprenorphine across the early and late periods. For example, answers to the question “How much did they make you want to use heroin?” and “How much did they excite you?”, changed from the early to the late scans.

Answers to “How much did you like them and want to see more of them?” seem puzzling at first, as participants wanted to see more of the neutral stimuli for both periods. Post-test interviews indicated that heroin-related stimuli increased their fear of being unable to maintain abstinence, thus leading to an avoidance of heroin-related stimuli, as reported in Hutcheson et al. (2001).

Brain regions found here showing activation to heroin-related cues were consistent with most literature studies using similar designs (Sell et al., 1999; Langleben et al., 2008; Zijlstra et al., 2009). These regions, including the VTA, ventral striatum/NAc, thalamus, OFC, prefrontal cortex, parietal cortex, amygdala and hippocampus, are known to play critical roles in reward, reinforcement, consciousness, paracentral lobule, precentral gyrus, postcentral gyrus, middle temporal gyrus and calcarine sulcus. Replacement therapy with buprenorphine clinically reduces withdrawal and craving for heroin (O'Brien, 2005; Srivastava and Kahn, 2006; Collins and McAllister, 2007), and supposedly alleviates negative reinforcement such as abstinence and heroin-related cues (Hutcheson et al., 2001; Dackis and O'Brien, 2005). Hence, these brain regions may be related to the desire for heroin due to negative reinforcement and can be modulated by buprenorphine as therapeutic targets.

Brain regions with an unchanged fMRI response to heroin-related cues from early to late periods included the ventral striatum, OFC, prefrontal cortex, parietal cortex, suggesting their responses were not modulated by buprenorphine. Therefore, they may be related to the limited therapeutic effects on relapse using buprenorphine.

The striatum is core of the reward system in addiction (Everitt and Robbins, 2005; Volkow et al., 2006b). The pattern of unchanged activation in the striatum may reflect sustained expectation of the high reward level of addiction drugs (Volkow et al., 2003b, 2006a). This would imply that, for more radical cure of addiction, the striatum should be targeted to degrade the already elevated reward level from drug abuse due to tolerance and sensitization (Nestler, 2009). Recent animal studies on the incubation of cocaine craving have indicated such a possibility to target the GluR2-lacking AMPA receptors in the ventral striatum (Conrad et al., 2008).

The orbital-prefrontal cortices including OFC and prefrontal cortex are known to be involved in motivation, drive, control, and inhibition (Wilson et al., 2004; Weiss, 2005; Volkow et al., 2009). The parietal cortex is known to be involved in impulsivity (Lee et al., 2005), attention (Lawrence et al., 2002), and craving (Garavan et al., 2000) in the addicts. These two regions should be important therapeutic targets for addiction as they may function together with the striatum to result in the persistence and uncontrollability of compulsive drug seeking.

As can be seen in Fig. 2, in brain regions showing activation changes such as amygdala, hippocampus, VTA and thalamus, the signals decreased for the heroin-related stimuli from the early to the late scans, but increased for the neutral stimuli. One way to understand this pattern is that drug vulnerability (Volkow et al., 2003a, 2004) may be associated with both increased saliency to drug or drug-related stimuli, and decreased saliency to drug-unrelated stimuli, and buprenorphine may take effect in both reducing the former and enhancing the latter. Additionally, be-
cause of these different or even opposite patterns of signal changes to different stimuli, the task repetition effect apparently cannot account for all our results (Grill-Spector et al., 2006).

One limitation of the present study is that plasma concentrations of buprenorphine were not measured, as most participants refused blood sampling more than twice during the short session, while samples for at least three time points were required to ensure statistical reliability. However, based on experimental data from previous studies of sublingual administration (Mendelson et al., 1999; Strain et al., 2004; Chawarski et al., 2005; Ciraulo et al., 2006), the theoretical pharmacodynamic course of sublingual buprenorphine ought to be applicable to our participants.

In the methadone study, Langleben et al. (2008) pointed out that the reduced responses to heroin-related cues could be caused by a combination of reduced drug expectancy and increased methadone plasma levels, and suggested further placebo-controlled studies to help dissociate the two. In the present study, the expectancy of buprenorphine had faded after its administration during the early period, and increased buprenorphine plasma levels remained to be the dominant effect. Whereas this study aimed at the acute effects of buprenorphine on early-abstinent heroin addicts, the placebo-control, double-blind design was not used, to ensure the cooperation of the subjects. As an uncontrolled trial, with relatively small sample, the findings of this study are preliminary and tentative.

Using phMRI, the present study examined the acute effects of sublingual buprenorphine on brain responses to heroin-related cues at a very early period of abstinence in heroin addicts. The results showed that replacement therapy with buprenorphine reduced brain activation in amygdala, hippocampus, VTA and thalamus due to acute abstinence and heroin-related cues, but did not affect activities in ventral striatum and orbital-prefrontal-parietal cortices. Consequently, the failure of replacement therapy suggests that the ventral striatum and orbital-prefrontal-parietal cortices should be targeted in developing therapies for drug addiction. The present study also demonstrates the usefulness of phMRI in providing objective physiological measures to combine with and to complement subjective behavioral evaluation for more productive research in drug addiction.

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