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# Thirsty heroin addicts show different fMRI activations when exposed to water-related and drug-related cues

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**Abstract**

Relapse to drug use is frequently preceded or caused by craving, an intense desire for drug. Advances in functional brain imaging techniques make it possible to directly investigate this special mental state in vivo and non-invasively. Extant imaging studies on craving have been mostly on cocaine which is the dominant drug abused in the U.S. Employing functional MRI, we examined substance specificity of the neural circuitry underlying craving for heroin. Heroin is the primary drug abused in south-east Asia and has, particularly, become a serious social problem for China in recent years. Following abstinence from water and drug, 14 active heroin addicts (all male, mean age 33.2 years, average drug use history 7.1 years) underwent scanning inside a 1.5T Philips MR scanner during exposure to water-related, drug-related, and neutral cues. Water-related cues elicited anterior cingulate activation (Brodmann's area BA 32/24). Drug-related cues activated bilateral inferior frontal cortex (BA 44/45), confirming the critical role of prefrontal cortex in drug craving. Results suggest heroin craving may involve different neural substrates than do desire from basic physiological drives, such as thirst. As the first fMRI study of heroin craving, our study adds to the scant but much-needed brain imaging literature on heroin addiction.


*Keywords:* Addiction; Craving; Drug-dependence; Heroin; Opiate; Functional MRI

## 1. Introduction

Substance abuse is a major health problem with far-reaching social, psychological and physical consequences. A high percentage of drug-dependent patients who completed detoxification programs relapse. Relapses are often preceded by craving, which can be described as a strong, persistent desire or sense of compulsion to drug-seeking behaviors, and patients often attribute craving as the cause for their relapses (Wise, 1988). Aiming at more effective relapse prevention, researchers have paid much attention to the study of craving, which was typically induced in laboratory settings with drug-related cues (Childress et al., 1986; Drummond et al., 1995). In response to these cues, addicts demonstrate physiological and subjective self-report evidence of drug-like effects, such as feeling high and constricted pupils.

However, as craving is a motivational mental state in highly functioning living systems, it was not until the advance of functional imaging techniques (Petersen et al., 1988; Kwong, 1995) when it is possible to directly investigate its neurobiology in vivo and non-invasively. A small but growing number of imaging studies have compared drug addicts and normal controls in their brain responses to drug-related cues, relative to neutral cues (Grant et al., 1996; Maas et al., 1998; Sell et al., 1999; Garavan et al., 2000; Wexler et al., 2001; Bonson et al., 2002). Frontal cortical regions including dorsolateral prefrontal cortex, orbitofrontal cortex, and anterior cingulate have been frequently implicated as associated with craving.

Among these imaging studies, as summarized in Wilson et al. (2004), there is more work on cocaine (eight papers) than on heroin (two papers). This is not surprising given that cocaine was proclaimed "the drug of greatest national health concern", with

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two million individuals in the U.S. addicted to cocaine, about four times the number addicted to heroin (Gawin, 2001). However, the last decade has witnessed a resurgence of heroin use in the adolescent population of the U.S. (Tarabar and Nelson, 2003). In U.K., opiate dependence leads to higher rates of morbidity than all other drugs of abuse (Lingford Hughes et al., 2003). And in south-east Asia, heroin is the primary drug abused and, in particular, has become the most serious public health problem in China in recent years. Clearly, research on heroin addiction is much needed to better understand its pathophysiology.

The few existing functional imaging studies on heroin craving (Sell et al., 1999, 2000; Daglish et al., 2001) were all performed with positron emission tomography (PET). Functional magnetic resonance Imaging (fMRI), based on blood oxygenation level-dependent (BOLD) contrast, is a relatively more accessible alternative to measure brain activation in response to stimuli, with its low-cost, high spatial/temporal resolution, and no need for radioactive tracers. In the present study, we evaluated whether regional cerebral activation to drug craving previously detected with PET in heroin addicts is also detectable with the BOLD imaging method.

In a well-cited fMRI study, Garavan et al. (2000) found that explicit sex scenes activated brain regions that overlapped with those activated by drug-related cues in cocaine addicts. Their results favor a view that the neural circuitry for craving may not be dedicated but shared by non-drug evocative stimulus. Thirst is, like sex, one of the three basic physiological drives that can be associated with intense desire. We wondered if similar neural substrates were involved for drug wanting and water wanting. To this end, we included a manipulation to make our participants feel thirsty and examined their BOLD responses to water-related cues.

## 2. Materials and methods

### 2.1. Participants

Fourteen active heroin users (all male, mean age = 33.2 years, age range 18–45 years) participated in this study. All had normal vision and were strongly right-handed as judged by a handedness inventory. They were native Chinese from the local community of Shantou University (Shantou, China) who were to be treated in a detoxification clinic. Their participation in this study was prior to their receiving any treatment from the clinic. No participant had psychiatric disorders other than heroin abuse or dependence. Their heroin use history averaged 7.1 years (range from 2 to 16 years). The average interval between successive drug use for the whole group within a 24-h period was 6.8 h (standard error 0.39, range from 4 to 12 h). The mean length of their prior-study heroin abstinence was 8.5 h (standard error 0.82, range from 5 to 13 h). Our interview data indicate that abstinence of this length induced moderate (3.5 out of a 1–5 scale) heroin craving for these participants. No water intake was allowed within the 6-h period before scanning. Forty-five minutes before the scanning, participants took 40 ml glucose (10%) solution and 2 ml furosemide to increase their level of thirst. Our pilot data show that these two measures combined reliably induced moderate level of thirst. Informed consent was obtained in accordance with guidelines from the Medical School of Shantou University.

### 2.2. Image acquisition

All MR imaging was conducted on a 1.5T Philips MR scanner with a standard headcoil at the Medical School of Shantou University. Twenty-three axial slices covering the whole brain were acquired with a $T2^*$-weighted gradient-echo echo planar imaging (EPI) pulse sequence (TR = 3000 ms, TE = 50 ms, flip angle = 90°) for the functional scans (acquisition matrix = 64 × 64, FOV = 230 mm × 230 mm, slice thickness = 4 mm, skip = 2 mm). Co-planar anatomical images (acquisition matrix = 256 × 256) were acquired with a T1-weighted spin echo pulse sequence (TR = 509 ms, TE = 14 ms).

### 2.3. Stimuli and procedure

Participants lay supine inside the scanner and wore goggles specially designed for MR environment. Their head was restrained with padding behind the neck and in between the head and the headcoil. They were told to keep their head still inside the scanner. The design was a block design. Each participant first underwent a structural scan and then two functional scans. In one functional scan, they fixated a central cross for 30 s before seeing one block of natural scene pictures (Neutral condition) which included 22 pictures presented one every 4 s. They then saw 30 water-related pictures for 120 s presented at the same rate (Thirst condition). The Thirst condition was followed by another block of Neutral condition with 22 pictures. The other functional run had the same structure except water-related pictures were replaced with drug-related pictures (Drug condition). The inclusion of a neutral period both before and after the drug/thirst cue period was to better control time-varying scanner noise. Participants were asked to passively view the pictures for later recognition. Eye-movement monitoring with an eye-tracking system confirmed that participants maintained attention during the scan. Natural scene pictures included flowers, toys, furniture, and street scenes. Water-related pictures included people drinking water, clean stream, and water in containers. Drug-related pictures included drug intake scenes and heroin pictures. We expect that the addict participants would be aroused by the drug cues, which would have a negative impact on their paying attention to the thirst cues, should the Thirst condition follow the Drug condition. Therefore, instead of randomizing condition order, we always put the Thirst condition before the Drug condition. To reduce the order effect this design is subject to, we contrasted the Drug/Thirst conditions with their own Neutral conditions (see next section).

### 2.4. Imaging analysis

Image analysis was carried out with SPM2 (Wellcome Department of Cognitive Neurology, London). Functional images were motion corrected, and coregistered to the co-planar anatomical image for each participant. The T1 images were

normalized to the standard SPM template and the resulting transformation matrix was applied to the coregistered functional images. Such normalized functional images, interpolated to 4-mm isotropic voxels and spatially smoothed with a Gaussian filter of 8-mm kernel, were entered into a regression analysis using the general linear model for block designs in SPM2.

In regressor construction for the multiple regression, each block was modeled with a square-waved epoch, convolved with the canonical hemodynamic response function in SPM. Three regressors were constructed, one for each condition. Session-specific effects were modeled as confound variables and low frequency noise in the signal was removed before the regression analysis. Following the regression analysis, two linear contrasts were constructed, Thirst versus Neutral and Drug versus Neutral. The Drug condition and the Thirst condition were each contrasted with their respective Neutral condition which pooled the neutral cue periods both immediately before and after their corresponding motivational cue period. Subject-specific estimates of the contrasts were obtained and then entered into a standard SPM second-level analysis with subject treated as a random effect, using one-sampled *t*-test (d.f. = 14,1). The expected mean difference value for the *t*-tests was set to zero.

A voxel-wise intensity threshold (uncorrected $p < 0.005$) and a spatial extent threshold (cluster size greater than 20 voxels) were combined to control for multiple comparisons in the generation of *t*-maps. Due to the explorative nature of this study, our threshold was more liberal than the commonly used $p < 0.001$. While being more sensitive for signal detection, this also increases the likelihood of false activation (Type I errors). All coordinates reported were in Talairach space converted from MNI space based on an algorithm at www.mrccbu.cam.ac.uk/Imaging/mnispace.html.

## 3. Results

Relative to the natural scenes, water-related cues elicited significant activation in anterior cingulated BA 32/24 (Fig. 1a). In comparison, drug-related cues elicited several regions including bilateral inferior frontal cortex (BA 44/45), left extra-striate cortex (BA 18), bilateral fusiform gyrus (BA 19), and bilateral cerebellum (Fig. 1b).

Among these two sets of regions identified, the anterior cingulate did not show significant activation for the Drug versus Neutral comparison and the frontal/occipital/cerebellar regions did not show significant activation for the Thirst versus Neutral comparison, even when we lowered the threshold to $p = 0.1$. This excludes the possibility that what we observed were simply artifacts from threshold setting (e.g., the anterior cingulate was also responsive to the drug cues except its activation happened to be just below the specific level of threshold we chose). This

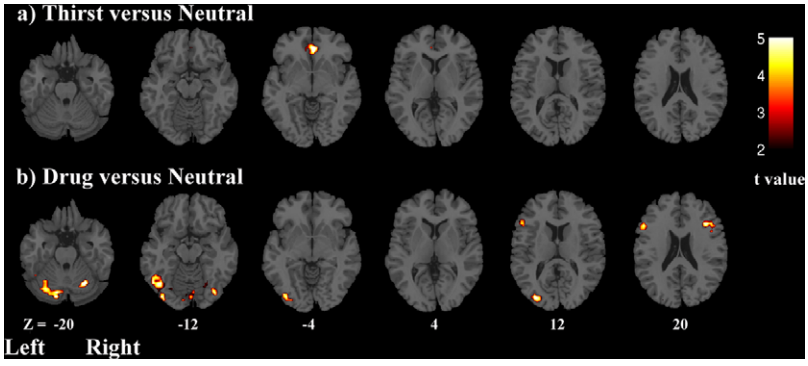


Fig. 1. Axial *t*-maps of brain activation ($p < 0.005$, minimum 20 contiguous voxels) for: (a) Thirst vs. Neutral comparison; (b) Drug vs. Neutral comparison. No deactivation was found in either comparison. The images were superimposed on a standard SPM anatomical template brain in neurological convention with *z* coordinate for each slice shown in Talairach space.

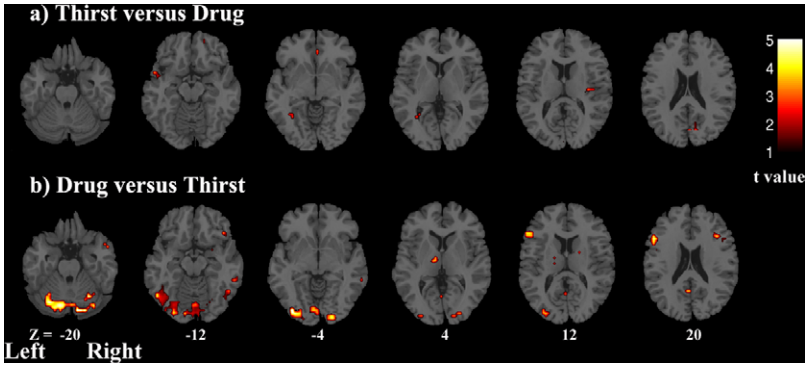


Fig. 2. Axial *t*-maps of brain activation ($p < 0.01$, minimum 20 contiguous voxels) for: (a) Thirst vs. Drug comparison; (b) Drug vs. Thirst comparison. Other details are the same as that for Fig. 1. Both the Thirst and the Drug conditions were corrected with their respective Neutral control conditions before the direct comparisons (see Section 2.4 for more details).

Table 1
Summary information for regions of activation revealed in the statistical contrasts

| Contrast | Anatomical structure | Brodmann's areas | Stereotaxic coordinates | | | Peak *t*-value | Volume (voxel) |
|---|---|---|---|---|---|---|---|
| Thirst > Neutral | Anterior cingulate | 32/24 | 3 | 38 | −5 | 6.6 | 39 |
| Drug > Neutral | L. Inferior frontal gyrus | 44/45 | −52 | 20 | 18 | 5.2 | 42 |
| | R. Inferior frontal gyrus | 44/45 | 46 | 23 | 19 | 5.9 | 41 |
| | L. Extra-striate cortex | 18 | −28 | −82 | 18 | 6.5 | 25 |
| | L. Fusiform gyrus | 19 | −44 | −63 | −10 | 6.5 | 62 |
| | R. Fusiform gyrus | 19 | 37 | −74 | −11 | 6.8 | 24 |
| | L. Cerebellum | – | −27 | −72 | −13 | 6.1 | 81 |
| | R. Cerebellum | – | 27 | −66 | −15 | 7.2 | 28 |
| | Cerebellum | – | 1 | −78 | −12 | 5.8 | 50 |

*Note:* Coordinates shown in Talairach space for the peak voxel in each activated region. Voxel size is 4 mm × 4 mm × 4 mm.

conclusion is further confirmed in the direct comparison results between the Drug and the Thirst conditions (Fig. 2) where both the anterior cingulate region exposed in the Thirst versus Neutral comparison and the frontal and occipital/cerebellar regions exposed in the Drug versus Neutral comparison remain statistically significant at a more lenient threshold of $p < 0.01$. (It is generally recognized that interactions have less statistical power than main effects.) More detailed information is presented in Table 1, including the volume of each activated region, the *t*-value and the Talairach coordinates of the corresponding peak voxel.

## 4. Discussion

Using PET, Denton et al. (1999a,b) showed that thirst sensation in normal subjects evoked significant activation in anterior cingulate and posited that this cortical region plays an important role in the genesis of thirst. The anterior cingulate activation we found accompanying desire for water is consistent with their hypothesis. One caveat is that our results only indicate an association between anterior cingulate activity and participants' being in a thirsty state. We do not claim that anterior cingulate is specific to the sensation of thirst. Anterior cingulate has been implicated in a large range of motor, cognitive and affective functions, such as conflict, empathy for pain, monetary reward (see Botvinick et al., 1999; Bush, 2004; Singer et al., 2004; Williams et al., 2004). It is quite possible that the activation of this area in the present study reflects some consequences from being thirsty.

While anterior cingulate was found associated with craving in 10 out of 19 imaging studies (Wilson et al., 2004), we did not find more activation in this region for drug-related cues than for neutral cues. Daglish et al. (2001) did report anterior cingulate activation, which, however, merged with a middle frontal gyrus activation not often seen in the literature. Sell et al. (1999) found anterior cingulate activity for craving, though only when participants were actually injected with heroin, but Sell et al. (2000) did not. It is possible that anterior cingulate may play a less important role in craving for heroin than for cocaine and other psychoactive substances.

As reviewed in Wilson et al. (2004), orbitofrontal cortex was found associated with craving (including for cocaine, opiate, alcohol, and cigarette) in some (6 of 18) imaging studies. Our failure in observing any activation in this region may be due to the low signal in this brain structure in EPI images from susceptibility related signal loss. Out of the three existing PET studies on opiate craving, one (Sell et al., 2000) reported orbitofrontal BA 11 activity for drug-related cues and two did not (Sell et al., 1999; Daglish et al., 2001).

The increased activity in visual cortex and cerebellum activation for drug-related cues than to neutral cues can be attributed to enhanced attention drawn to these stimuli of high emotional valence to the patients, as shown in previous craving studies (e.g., Grant et al., 1996; Sell et al., 1999) and studies with more general emotional stimuli (e.g., Hamann et al., 2002).

The inferior prefrontal activation found in the present study was close in location to the dorsolateral prefrontal cortex reported in Sell et al. (1999) which crossed with/without heroin injection with drug-related/neutral stimuli in a 2 × 2 factorial design. Their major finding was a midbrain activation associated with both the main effect of stimulus type and that of heroin injection. The differential prefrontal activation to drug-related videos relative to neutral ones was only evident when there was heroin injection. Sell et al. (1999) did report a left inferior prefrontal activation for craving at BA 47, more inferior to what we found. In the Daglish et al. (2001) study, no prefrontal activation was found for craving except for a left medial frontal areas merging with left anterior cingulate. A few imaging studies on cocaine showed dorsolateral prefrontal activation typically around BA 9 but not in BA 44/45 (Grant et al., 1996; Maas et al., 1998; Garavan et al., 2000).

Briefly, the present results showed an important role of prefrontal cortex in heroin craving, consistent with previous imaging work on heroin and cocaine addiction. However, "disappointing inconsistencies" (Wilson et al., 2004) also exist, which are currently difficult to resolve due to the small literature and the much-varied methodologies across studies. There are signs that the neural activities for heroin craving may be different from that for cocaine craving, a topic needing further investigation.

Researchers have also started identifying variables that could explain some of the inconsistency in the literature. One factor Wilson et al. (2004) found useful was participants' expected drug accessibility during or after the study. With the Chinese law enforcement on heroin injection, participants in our study were aware of drug unavailability in the study. Under such circumstances, they may, as Wilson et al. pointed out, have tried

to suppress cue-induced craving through engaging inferior prefrontal cortex, which has been linked with inhibition in the imaging literature (Zhang et al., 2004).

Garavan et al. (2000) asked experienced cocaine users and control subjects to view films portraying neutral outdoor scenes, individuals smoking crack cocaine, and explicit sex content and found that majority of the areas (10 out of 13) identified for cocaine craving showed stronger activation for sex films than for neutral films. They suggested that cocaine craving is associated with neuroanatomical circuitry sensitive to evocative stimuli, drug-related or not. Thirst is, along with hunger and sex, one of the three basic physiological drives that can be associated with intense desire.

Following Garavan et al., one might speculate that craving for water may share neural substrates with that for drug. However, our results did not support this conjecture. Desire for water in our thirsty participants seem to be related to anterior cingulate while craving for heroin to inferior prefrontal cortical areas. Desire or craving for different types of stimuli may not always share the same underlying neural substrates. One possibility is that thirst may be of a different nature from sex and drug in that it is purely physiological while the latter two could induce a combination of physiological as well as psychological effects.

Following the scanning session, participants were interviewed. Although no rating data were collected, 6 out of the 14 participants reported feeling of thirst and 7 wanting for drug. This proportion seems lower than one would expect for classifying the present study as one on craving and suggests a framing our results in terms of 'cue-reactivity'. Alternatively, it may reflect a weakness in our design where participants were not explicitly encouraged to entertain the feelings evoked by the cues. They may have suppressed their feelings to show their treatment-seeking attitude, a factor that has been considered relevant in imaging studies of addiction (Wilson et al., 2004).

One weakness of the present study is that the Drug condition and the Thirst condition were not equivalent in that thirst was enhanced by water abstinence combined with drinking glucose/furosemide solution but drug craving was induced from heroin abstinence only without injection of any opiate antagonist. Such treatment difference may have led to differences in the two motivational states and undermine interpretation of our results.

Heroin, being one of the most addictive drugs abused, carries significant morbidity and mortality. However, its effective treatment remains elusive. Functional imaging, particularly the fMRI technique which is much more widely accessible and much less expensive than PET, has been considered a valuable tool to understanding the neurobiological mechanisms of drug dependence. Our results show an important role of prefrontal cortex in heroin craving and suggest that heroin craving may involve different neural substrates than do desire from basic physiological drives. To our knowledge, there has not been any fMRI study examining craving in heroin addicts. The present study adds to this scant but much-needed brain imaging literature on heroin addiction to meet the challenges one of the "hardest" drugs present.

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