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Research Report

Distinct resting-state brain activities in heroin-dependent individuals☆

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ABSTRACT

Previous functional imaging studies on heroin addicts have focused on abnormal brain functions based on specific tasks, while few fMRI studies concentrated on the resting-state abnormalities of heroin-dependent individuals. In the current study, we applied the pattern classification technique, which employs the feature extraction method of non-negative matrix factorization (NMF) and a support vector machine (SVM) classifier. Its main purpose was to characterize the discrepancy in activation patterns between heroin-dependent individuals and healthy subjects during the resting state. The results displayed a high accuracy in the activation pattern differences of the two groups, which included the orbitofrontal cortex (OFC), cingulate gyrus, frontal and para-limbic regions such as the anterior cingulate cortex (ACC), hippocampal/parahippocampal region, amygdala, caudate, putamen, as well as the posterior insula and thalamus. These findings indicate that significant biomarkers exist among the network of circuits that are involved in drug abuse. The implications from our study may help explain the behavioral and neuropsychological deficits in heroin-dependent individuals and shed light on the mechanisms underlying heroin addiction.

1. Introduction

Drug addiction, is characterized by a compulsive drive to take drugs despite serious negative consequences and is a disorder that involves complex interactions between biological and environmental variables (Volkow et al., 2003). Over the past few decades, numerous imaging studies have revealed neurochemical and functional changes in the brains of drug-

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addicted subjects (Fu et al., 2008; Lee et al., 2005; Li and Sinha, 2008; Liu et al., 2009; Yuan et al., 2009, 2010a, 2010b). It has been found that in heroin-dependent individuals there is increased white matter intensity in the frontal area and decreased gray matter density in the bilateral prefrontal cortices and in the temporal regions compared to healthy subjects (Lyoo et al., 2004; Yuan et al., 2009). Cognitive performance impairments in heroin-dependent individuals have also been verified in a variety of tasks, such as response inhibition and decision-making (Fu et al., 2008; Lee et al., 2005). Recent resting-state functional magnetic resonance imaging (fMRI) studies have also reported abnormal functional connectivity and topological properties in heroin-dependent individuals (Liu et al., 2009; Ma et al., 2010; Yuan et al., 2010a,b). All of these findings provide new insights into the mechanisms underlying addiction.

During a standard fMRI experiment, hundreds of volumes of brain activations in thousands of locations are acquired. Thus, a wide range of multivariate statistical methods are frequently being applied to the analysis of an fMRI time series (Liu et al., 2010; Zhang et al., 2009a,b). In contrast to the strictly location-based conventional analysis, previous studies (Cox and Savoy, 2003; Haxby et al., 2001; Haynes and Rees, 2005b, 2006; Kamitani and Tong, 2005; LaConte et al., 2005; Mitchell et al., 2003, 2004) showed that the sensitivity of functional neuroimaging can be dramatically increased by taking into account the full spatial pattern of brain activations measured simultaneously at many locations. Given the goal of detecting the presence of a particular mental representation in the brain, the primary advantage of pattern-based analyses compared with the conventional univariate approach is increased sensitivity. The information available at each location can be accumulated in an efficient way across many spatial locations. Even if two single brain regions do not individually carry information about a cognitive state, they might express brain activation when jointly analyzed (LaConte et al., 2005). This approach has many other additional advantages as well. It does not employ unnecessary steps such as spatial smoothing, which might remove the fine grained spatial information about perceptual or cognitive states. By avoiding the loss of information of the functional state in the brain at any given time point, the MVPA greatly increases the sensitivity of decoding the critical brain activity related to a person's perceptual or cognitive state (Haynes and Rees, 2005a; Polyn et al., 2005).

Volkow et al.(2003) proposed a model consisting of four circuits involved in drug abuse and addiction: (1) reward, located in the nucleus accumbens (NAc) and ventral pallidum; (2) motivation/drive, located in the orbitofrontal cortex (OFC) and subcallosal cortex; (3) memory and learning, located in the amygdala and hippocampus; and (4) control, located in the prefrontal cortex and anterior cingulate gyrus (ACC). In this model, drug addiction was considered as a state initiated by the qualitative reward value of the drug, which triggers a series of adaptations and changes in reward, motivation/drive, memory and control circuits of the brain. These functional changes result in an enhanced and permanent saliency value for the drug and loss of inhibitory control, which eventually leads to the emergence of compulsive drug administration and relapse. These identifications designate the complexity of drug addiction and the interactions of multi-neural circuits (Dackis and Gold, 1985; Gold et al., 2009). Pattern-based multivariate analyses aim to account for the full spatial patterns of brain activity systematically, as well as for the wide variety of external influences. Compared to the location-based conventional univariate method, the pattern based approach is far more suitable to distinguish the framework of the neural network between addicts and healthy controls.

We hypothesized that there exist significant biomarkers among the network of four circuits (reward, motivation/drive, memory/learning and control) as well as other brain areas, which are involved in drug abuse and addiction according to Volkow's model (Volkow et al., 2003). Furthermore, we also hypothesized that pattern classification analyses could reveal subtle differences in the neural responses. In view of the advantages of the multivariate method, we utilized the pattern classification technique (multi-voxel pattern analysis, MVPA) in the current study to analyze the addiction fMRI data sets and to characterize the discrepancies in activation patterns between heroin-dependent individuals and healthy subjects during the resting state. With the goal of decomposing the multivariate data as non-negative factors, the non-negative matrix factorization (NMF) technique was employed to extract features and the support vector machine (SVM) was then utilized to classify the features, respectively.

2. Results

We trained and tested the classifier to distinguish the patterns of the neural responses between heroin-dependent individuals and healthy controls. Table 2 and Fig. 1 summarized the brain areas with significant discriminating accuracies higher than the threshold of the discriminating level (65%, $P<0.01$, which is higher than the chance level of 50%) (Cox and Savoy,

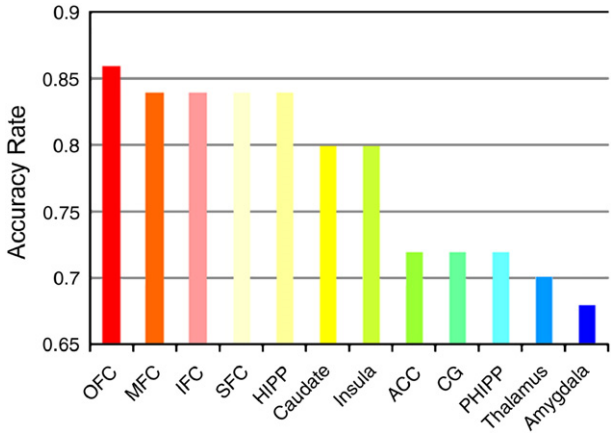

Fig. 1 – The mean accuracy rate between the heroin-dependent individuals and healthy controls in the brain. Abbreviations: OFC, orbitofrontal cortex; MFC, medial frontal cortex; IFC, inferior frontal cortex; SFC, superior frontal cortex; HIPP, hippocampus; ACC, anterior cingulate cortex; CG, cingulate cortex; PHIPP, parahippocampus.

2003; De Martino et al., 2008). The various brain regions listed on the horizontal axis are displayed from highest (0.86) to lowest (0.68) values of accuracy rate as shown on the vertical axis (Fig. 1). Spatial maps of classifier accuracies are shown in Fig. 2. Distinct areas of the brain with high accuracies were found in the orbitofrontal cortex (OFC, Brodmann Area (BA) 10), cingulate gyrus (CG, BA 32), frontal and para-limbic regions such as the anterior cingulate cortex (ACC, BA 24), hippocampal (HIPP)/parahippocampal (PHIPP) regions, amygdala, caudate, putamen, as well as the posterior insula (BA 13) and thalamus. Among these structures, the OFC is involved in the motivation/drive circuit; the ACC and CG participate in the activity of a control network; the MPFC is concerned with the reward circuit; while the amygdala, HIPP, PHIPP, and putamen take part in the activity of the memory network.

3. Discussion

We applied the MVPA to explore the distinct neural response patterns between heroin-dependent individuals and healthy controls. The results demonstrated that significant differences exist in the medial PFC, ACC, OFC, caudate, putamen, HIPP and prefrontal cortex. These regions are related to the networks of reward, motivation, memory/learning and control circuits, respectively. These discoveries are consistent with the four circuits involved in the model representing drug abuse and addiction, as proposed by Volkow et al.(2003). In addition, the thalamus and insula were also identified since they may participate in various roles within the network modeling addiction.

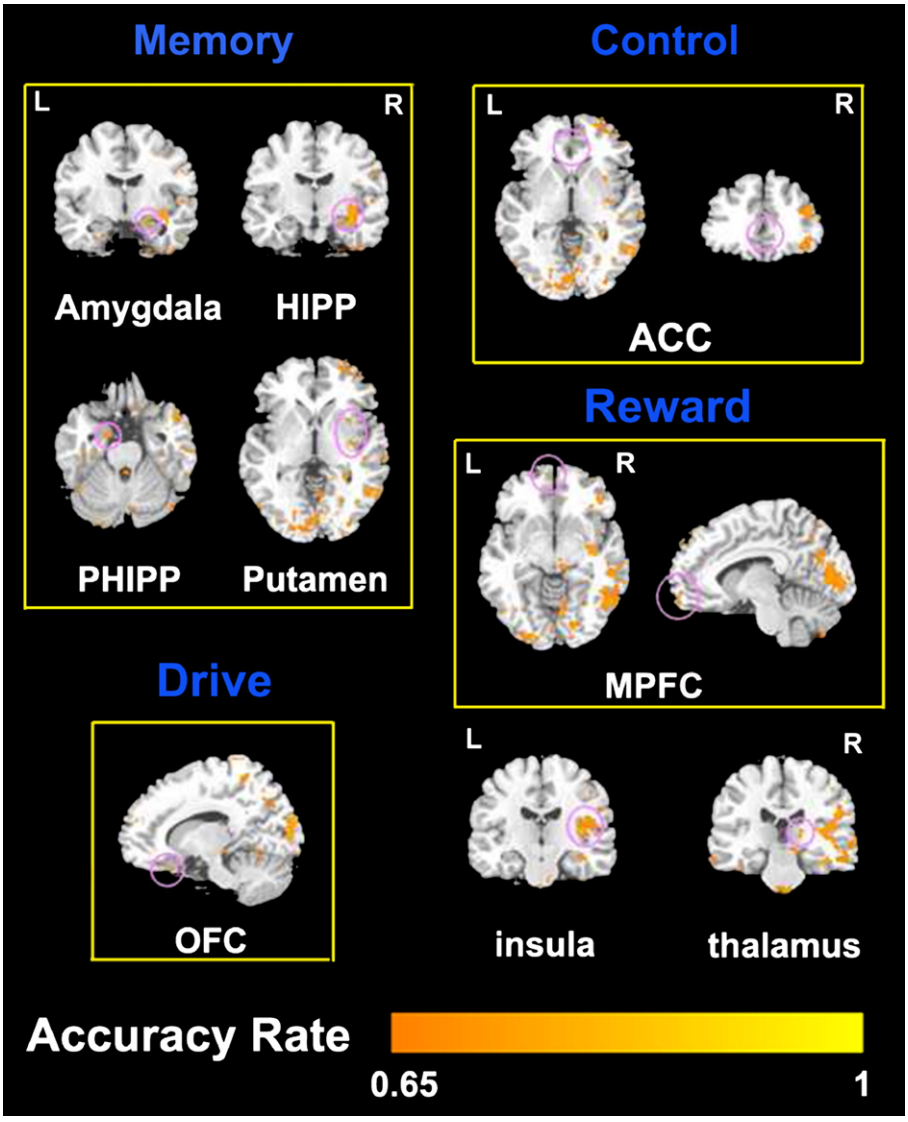

Fig. 2 – Spatial maps of classifier accuracies for distinguishing the neural response between heroin-dependent individuals and healthy controls. They are mainly located in the OFC, MPFC, ACC, HIPP/PHIPP, amygdala, caudate, putamen, as well as the posterior insula (BA 13) and thalamus. These regions belong to a proposed network of four circuits (reward, drive, memory and control) involved with addiction respectively (Volkow et al., 2003). Abbreviations: OFC, orbitofrontal cortex; MPFC, medial prefrontal cortex; ACC, anterior cingulate cortex; HIPP, hippocampus; PHIPP, parahippocampus; BA, Brodmann area.

Studies in drug-addicted subjects have consistently shown a long-lasting decrease in the number of dopamine (DA) D_2 receptors in drug abusers compared to controls (Volkow et al., 2002), and heroin addiction and cocaine abusers have also shown decreased DA cell activity (Dackis and Gold, 1985; Volkow et al., 1997; Wang et al., 1997). The decrease in the number of DA D_2 receptors coupled with the decrease in DA cell activity should result in a decreased sensitivity of reward circuits and lead to decreased interests in ordinary environmental stimuli. Ultimately, many drug addicts seek drug stimulation as a means to temporarily activate these reward circuits. Several studies (Oswald et al., 2005, 2007; Pruessner et al., 2004) investigated the ventral striatum (VS), which contains the nucleus accumbens (NAc), and these studies suggested that the VS also plays a role in stress in addiction due to its involvement in reward processing. Stress has consistently shown an increase in drug craving and compulsive drug seeking in cocaine-addicted individuals, and there has been a greater sensitivity to stress-induced craving and arousal in cocaine patients as compared to the corresponding controls (Fox et al., 2008). In the current study, we found significant differences in the medial prefrontal cortex (PFC) and ACC between heroin-dependent individuals and healthy subjects. Since the medial PFC and ACC play a role in stress and reward processing, this raises the possibility of an interrelationship between the VS and the ACC. There are cortical inputs from the PFC to the VS, which also interact between the VS and the amygdala by receiving cortical afferents (Voorn et al., 2004). A lesion of the medial PFC in laboratory animals decreases the reinstatement for a response to the drug with exposure to stress, drug-related cues and the drug itself (Kalivas and McFarland, 2003). These studies suggested that the PFC may exercise some control over instrumental learning and drug response. We postulated that the PFC may regulate VS activity particularly under conditions of stress and that stress contributes to motivation for drug use and abuse.

Another area of the brain that indicated significant differences between groups is the OFC. Imaging studies showed that the OFC appears to be hypoactive in drug-addicted subjects tested during withdrawal (Adinoff et al., 2001), indicating a lack of stimulation by salient stimuli during detoxification. In contrast, in active cocaine abusers, the OFC has been shown to be hypermetabolic in proportion to the intensity of the craving experienced by the subjects (Volkow et al., 1991). Thus, exposure to the drug or drug-related stimuli during the withdrawal state reactivates the OFC and results in compulsive drug intake. Similar activation of the OFC has been reported during exposure to drug-related cues when it has also elicited craving (Volkow and Fowler, 2000). Since an increased OFC activation has been associated with compulsive disorders (Insel, 1992), Volkow et al. (2003) postulated that the activation of the OFC in addicted subjects contributes to compulsive drug intake. Preclinical studies have shown that damage to the OFC results in a behavioral compulsion to procure the reward even when it is no longer reinforced (Rolls, 2000). Since the OFC also processes information associated with the prediction of reward, its activation during cue exposure could signal reward prediction. Additionally, this OFC activation could also be experienced as a craving to the addicted subject during detoxification by consequently reducing the number of DA D_2 receptors in the striatum (Volkow et al., 2001). Since DA D_2 receptors transmit the reward signal to the OFC, this association could be interpreted as a disruption of the OFC, secondary to changes in striatal DA activity.

Learning and memory are relevant to addiction in terms of the recovery process. Often a place, or a person, or an event, or even a very simple cue can bring back undesirable memories and trigger an intense desire for the drug, especially when the addict is trying hard to stay away from it. Among the multiple memory systems which were proposed to be involved in drug addiction, our discoveries included two of them: 1) habit learning, which is mediated in part by the caudate and the putamen, and 2) declarative memory, which is mediated partially by the HIPP (White, 1996). Through habit learning, well-learned sequences of behavior are elicited automatically by the appropriate stimuli. Declarative memory is related to the learning of affective states relative to drug intake. Memory circuits are likely to influence the effects of the drug during intoxication, since they set the expectations of the drug's effects in the addicted subject (Kirk et al., 1998). Activation of regions linked with memory has been reported during drug intoxication (Breiter et al., 1997) and during craving induced by drug exposure, video, or recall (Kilts et al., 2001). Cocaine-dependent patients had increased activity in the caudate and dorsal striatum compared to controls, and their activities were associated with drug cue-induced cocaine craving (Volkow et al., 2006). Greater craving-related activation in the dorsal striatum was consistent with the hypothesis that this region plays a key role in the transition from instrumental learning to habit learning, and it is also involved in driving compulsive drug seeking in addicts (Everitt and Robbins, 2005). Findings from human experiments, non-human primates and rats were consistent with the suggestion that declarative learning is mediated by a neural system that includes the HIPP and may describe complex cognitive learning in humans. Learning in the hippocampal system occurs very rapidly with relatively little experience. This property is important for understanding the development of addictive behavior. The HIPP is a critical structure within a neural network in the brain that can quickly acquire general information about all of the situations experienced. Information stored in this system includes knowledge of relationships among external events relevant to the situation in which a drug is obtained. Thus, declarative learning can contribute to the addictive process at this general level.

One of the most consistent findings from the current study is that there exists a distinction between heroin-dependent individuals and controls in the prefrontal cortex, including the cingulate gyrus, rostral ACC (rACC, BA 24), and right inferior and medial frontal gyri (Goldstein and Volkow, 2002). The prefrontal cortex is involved in decision making and in inhibitory control (Royall et al., 2002), and thus, its disruption could lead to inadequate decisions that favor immediate rewards over delayed but more favorable responses. This finding could also explain the impaired control over the intake of the drug even when the addicted subject expresses the desire to refrain from taking the drug (Goldstein and Volkow, 2002). Employing a go/no-go task, Kaufman et al. (2003) found cingulate and medial frontal hyperactivation during successful no-go inhibitions and errors of commission in cocaine

patterns compared to healthy controls, and further suggested that cocaine addiction is accompanied by disruption of neural circuitry critical for cognitive control. In particular, by contrasting successful and unsuccessful inhibitions, Rubia et al. (2005) identified the right inferior frontal cortex as a specific mediator for response inhibition. The rACC plays a control-level and perhaps a cross-modal role in mediating response inhibition. One study (Li and Sinha, 2008) indicated that the abstinent patient with cocaine dependence showed decreased activation in the rACC during stop signal inhibition. Furthermore, in cocaine-dependent patients the activity of the rACC was correlated with their subjective rating of difficulty in impulse control as assessed by the Difficulty in Emotion Regulation Scale (DERS) (Gratz and Roemer, 2004). Their finding extends to the previous work of Hester and colleagues by ascertaining the functional specificity of ACC hypoactivation in patients with cocaine dependence (Hester and Garavan, 2004).

In the current study, we analyzed and explained the data from the perspective of the network in cognitive neuroscience, instead of elaborating on the role of cortico–striatal pathways and compulsory drug use behavior. These findings are consistent with the model proposed by Volkow et al.(2003). During drug intoxication, the increase in activation of the DA-regulated reward circuit results in hyperactivation of the motivational/drive and memory circuits, which deactivate and remove the control exerted by the frontal cortex (Di Chiara, 2002). Without the inhibitory control, a positive feedback loop is set forth which results in compulsive drug intake. Because the interactions between the circuits are bidirectional, the activation of the network during intoxication serves to further strengthen the saliency value of the drug.

Although specific brain regions associated with each circuit were identified, we realized that other brain areas (such as the thalamus and insula) were involved in these circuits. One region may participate in more than one circuit (CG in both control and motivation/drive circuits), while the other brain regions and circuits (attention and emotion circuits) are likely to be affected in drug addiction. In addition, all of the above networks as well as the brain areas shown in Fig. 2 illustrate the various distinctions between heroin-dependent individuals and healthy controls by displaying a 3-dimensional spatial map representing the accuracy rate. Hence, the accuracy rate was used as a threshold to evaluate the differences between the two groups; therefore, it could also be recognized as a biomarker to judge the degree of their differences or even the degree of heroin-dependent subjects.

There are several potential limitations of our study. One limitation is the low number of heroin-dependent subjects. We recruited these subjects from a local methadone replacement therapy center. Most of the heroin addicts were not willing to take part in the study and we have strict inclusion and exclusion criteria. All of these factors resulted in a low number of subjects. The second limitation is that there are only male heroin-dependent subjects. Because there were very few female patients in the treatment center, no female subjects were recruited and the results of our current study may contain a gender bias. The third limitation of our study is that we did not consider the influence of cigarette smoking among the heroin-dependent subjects, especially considering that the tobacco smoking prevalence in heroin addicted subjects is currently 99.2% (Pajusco et al., 2011). Thus, future studies should consider attempting to distinguish the patterns of brain activation related to cigarette smoking separately from the effects of heroin dependence.

In this study we applied the pattern classification approach of MVPA to analyze the addiction fMRI data sets. With the help of the feature extraction method of NMF and the SVM classifier, we characterized the discrepancies in activation patterns between heroin-dependent individuals and healthy subjects during the resting state. These results verified our hypothesis about the networks of the four circuits involved in drug abuse and addiction according to Volkow's model (Volkow et al., 2003), and proved that the pattern-based approach is effective in analyzing them systematically. It also provided useful information for therapeutic interventions and suggested that more attention should be given to the patterns of information transmission and processing between these four circuits in heroin-dependent individuals. These findings may shed light on the mechanism underlying heroin addiction.

4. Experimental procedures

4.1. *Participants*

The study was performed on 12 abstinent male (right-handed, age 37.2±7.3 years, range 25–47 years) heroin-dependent patients. They were recruited from a local methadone replacement therapy center that had very few female patients. The experimental protocol was approved by the Institutional Review Board of The Fourth Military University, China. They were screened by the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) to confirm the diagnosis of opiate dependence. Exclusion criteria included psychiatric, neurological, and medical disorders requiring immediate treatment or a current state of any form of addiction with a diagnosis of substance abuse/dependence. The selected heroin-dependent individuals had a mean heroin abuse history of 89.5± 55.7 months (range, 19–182 months), a mean daily heroin consumption of 0.6±0.3 g (range, 0.2–1.5 g), and a mean abstinence from heroin of 4.9±0.8 months (range, 3–6 months). They all tested negative for the presence of morphine in the urinalysis (reagent box product by China Carrie City International Engineering Co.), as shown in Table 1. They all appeared to be in good physical health and did not display any overt behavioral signs of heroin intoxication.

Thirteen healthy right-handed male individuals (age-, education- and gender-matched, $P<0.05$; age 36.8±7.4 years, range 26–51 years) were enrolled from the local community to participate in the control group. None of the subjects were taking prescription drugs that affected the central nervous system within 1 week of scanning and none had a history of neurological illness. All subjects were fully informed of the nature of the research and had authorized written consent. Information regarding the demographic and clinical information of the heroin-dependent individuals and healthy subjects is presented in Table 1.

Table 1 – Demographic and clinical characteristics of heroin-dependent individuals and healthy controls.

	Healthy controls (mean/SD)	Heroin-dependent individuals (mean/SD)
Age (years)	36.8±7.4	37.2±7.3
Education (years)	9.1±3.2	9.8±2.5
Duration of heroin use (months)	N/A	89.5±55.7
Dosage of heroin use (g/day)	N/A	0.6±0.3
Duration of abstinence from heroin (months)	N/A	4.9±0.8
Methadone dose on the day of scanning (mg)	N/A	34.2±18.7

Abbreviation: SD, standard deviation.

4.2. *fMRI data acquisition*

The experiment was carried out in a 3T GE (Medical Signa EXCITE) scanner. Prior to the functional run, a high-resolution structural image for each subject was acquired using three-dimensional MRI sequences with a voxel size of 1 mm^3 and with an axial Fast Spoiled Gradient Recalled (3D-FSGPR) (TR 500 ms, TE 7.7 ms, matrix 256×256, field of view 220 mm×220 mm, 25 slices, 4 mm thickness, 1 mm inter-slice gap). A gradient echo T2*-weighted sequence with in-plane resolution of 3.75 mm×3.75 mm (TE 30 ms, TR 2 s, matrix 64×64, field of view 240 mm, and flip angle 90°) was also acquired. One hundred fifty echo-planar volumes were acquired during the resting scan and functional image scanning lasted 5 min. Subjects were instructed to close their eyes but remain awake during the entire scanning procedure. After scanning, all of the subjects reported that they had remained awake during the full length of the scan.

Table 2 – The results displayed high accuracies (65%, $P<0.01$, which is higher than the chance level of 50%) in the OFC (BA 10), CG (BA 24), frontal and para-limbic regions such as ACC (BA 24), HIPP/PHIPP region, amygdala, caudate, putamen, as well as the posterior insula (BA 13) and thalamus.

Position	Hem	BA	Talairach			Accuracy rate
			x	y	z	
OFC	R	10	39	54	21	0.86
MFG	R	9/46	41	48	11	0.84
IFG	R	44/45/46/47	42	41	6	0.84
SFG	R	9	43	52	15	0.84
ACC	R	24	5	29	10	0.72
CG	R	32	14	16	20	0.72
Caudate	R		15	15	13	0.8
Putamen	R		23	13	2	0.72
HIPP	R		35	−11	−15	0.84
PHIPP	L		-15	−3	−25	0.72
Amygdala	R		26	−7	−12	0.68
Insula	R	13	43	15	3	0.8
Thalamus	R		18	−24	11	0.70

Abbreviation: OFC, orbitofrontal cortex; BA, Brodmann Area; CG, cingulate gyrus; ACC, anterior cingulate cortex; HIPP, hippocampus; PHIPP, parahippocampus; MFG, medial frontal gyrus; IFG, inferior frontal gyrus; SFG, superior frontal gyrus.

4.3. *Image analysis*

Imaging data were preprocessed and analyzed using Statistical Parametric Mapping 5 (SPM5, http://www.fil.ion.ucl.ac.uk/spm). Images were first corrected for within scan acquisition time differences between slices and then realigned to the first volume to correct for interscan head motions. Upon reviewing the translation and rotation of the images, head movements greater than 1 mm or head rotations greater than 1° were discarded (one of the heroin-dependent patients was excluded). Next, we spatially normalized the realigned images to the standard EPI template and resampled them to a voxel size of 3 mm×3 mm×3 mm. Finally, the normalized data sets were filtered by using a bandpass filter (0.01–0.1 Hz). Spatial smoothing was not applied because this conventional preprocessing step could have removed fine-grained spatial information potentially useful for pattern classification analysis of MVPA.

The basic MVPA method is a straightforward application of pattern classification techniques, where the patterns to be classified are vectors of voxel activity values (Norman et al., 2006). The performance of MVPA analysis typically depends on three steps: feature selection, feature extraction, and classifier training and testing. First, feature selection decides which voxels will be included in the classification analysis. Secondly, feature extraction reduces the data matrix and extracts the eigenvector as the feature vector. Lastly, classifier training involves feeding a subset of these patterns into a multivariate pattern classification algorithm. In the current study, we used a novel variant of the "searchlight" approach (Kriegeskorte et al., 2006) to select an appropriate set of voxels in order to define multivariate features as the input of the pattern classification analysis. We defined a spherical multivariate "searchlight" centered on each voxel to combine the signals from all of the voxels of the gray matter that were included, and this "searchlight" was moved through the whole brain cortex. Therefore, this multivariate feature selection method can evaluate sets of voxels based on the information from percentage changes in the blood oxygenation level dependent (BOLD) signal over those voxels (Norman et al., 2006). The classification performance of each voxel shows how well the multivariate signal in the local spherical neighborhood differentiated the distinct patterns.

We first defined a small spherical cluster with a 6 mm radius comprised of 33 voxels (according to the "searchlight" with optimal or near-optimal detection performance) (Kriegeskorte et al., 2006) with each given voxel v_i spanning a width of 3 mm in each dimension. We extracted the unsmoothed data for each voxel in the fixed local cluster to yield a feature vector for this central voxel v_i, and a single feature was defined by x_{tj} which was the signal of a voxel j at a given time point t. Therefore, we acquired a data matrix $X=T\times V$ where T was the number of time points of each run and V was the number of voxels in this spherical cluster. We then applied the NMF technique (Lee and Seung, 1999), which is characterized by decomposing the multivariate data set as non-negative factors, to extract its eigenvectors. This approach is more compatible for analyzing fMRI data compared to other methods such as principal

component analysis (PCA) and singular value decomposition (SVD) because it enforces the constraint that the decomposed factors must be non-negative (must be equal to or greater than zero). Consequently, this characteristic fulfills the requirement for the guidelines of image processing.

Numerous classification algorithms have been developed and applied in MVPA studies. Here, we introduced the SVM (Cox and Savoy, 2003; Kamitani and Tong, 2005) approach which has already been successfully used in fMRI studies (Cox and Savoy, 2003). The classification was performed with the LIBSVM implementation (http://www.csie.ntu.edu.tw/wcjlin/libsvm). The SVM classifier is trained by providing examples of the form $\langle x, y \rangle$ where x represents a spatial pattern, which in our case is the final feature vector of each subject, and y is the category label ($y=1$ for a heroin-dependent individual and $y=-1$ for a healthy subject). We evaluated the performance of the classifier using the leave-one-subject-out cross validation test. The proposed approach here had k-folds where k (equals 24) is the number of all of the subjects involved. For each fold, we assigned the feature of the $k-1$ subjects obtained from the "searchlight" centered on voxel v_i to a "training" data set that was used to train this linear classifier. Then, the category label of the central voxel v_i belonging to the other subject (test data) was predicted by classifying it as the feature vector using the trained classifier. In total, the training and test procedures were repeated 24 times. Each test used feature vectors with $k-1$ different runs/subjects assigned as a training data set and a feature vector of a different run/subject assigned as the test data set. The classifier accuracy was measured by the proportion of runs correctly classified for the central voxel v_i. Thus, the mean classifier accuracy would yield v_{im} by averaging all of the accuracies calculated for every fold of this k-fold cross-validation procedure. The same procedure was then repeated for the next spatial position at v_i. The mean for the decoding accuracy of each voxel was then used to create a 3-dimensional spatial map representing the decoding accuracy for each position v_i in the whole brain and would thus represent the statistical differences between the two groups.

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