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Neural activity associated with cognitive regulation in heroin users: A fMRI study

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Abstract

Previous research has found heroin addicts to be impulsive. This study employed functional magnetic resonance imaging technology to investigate the differences between heroin addicts and normal controls in neural activity associated with cognitive regulation of behavior. Twenty-one Chinese men participated in this study, 11 of whom were newly admitted heroin-addicted patients and 10 of whom were healthy volunteers. In the experimental task, the subjects were required to first identify the correct directions of arrowheads and then give the opposite answers. Behaviorally, the heroin-dependent patients took a much shorter time to complete the more demanding second part of the task but committed more errors than the normal controls. This pattern of behavior, characteristic of people who are disinhibited and who tend to be impulsive, was consistent with previous reports of impulsivity observed in people who have abused heroin. The neural activity of the patients that was associated with performing the experimental task of cognitive regulation was different to that of the normal controls in terms of the pattern of prefrontal activation, the attenuation of activity in the anterior cingulate, and the additional recruitment of the right inferior parietal region. This study is the first that seeks to understand the neural activity associated with impulsive behavior in people who abuse heroin. The pattern of imaging data obtained resembled the pattern of data observed in immature brains attempting to exercise cognitive control of behavior. Further theoretical and clinical implications of the findings are discussed.

Keywords: Heroin; fMRI; Impulsive behavior; Addiction; Inhibition; Opioid; Cognitive regulation

Neuropsychological consequences associated with heroin use are common. One of these consequences reported is poor impulse control. Donovan et al. [6] found heroin addicts to have a distinctive hostility and alienation. Kim [15] reported the effectiveness of opioid antagonists in the treatment of impulse-control disorders. Pau et al. [20] and Lee and Pau [18] also observed that heroin addicts did have a significantly lower degree of impulse control than normal controls. Heroin addicts have also been found to make more false alarm error responses to non-targets on response suppression tasks [27].

Impulse control relies on the efficient operation of the prefrontal-cingulate network, which is important for performance monitoring and the inhibition of goal-irrelevant behavior [1,17]. However, frontal regions seem to be particularly vulnerable in heroin users (e.g. [3]). Danos et al. [5] observed hypoperfusion of the frontal regions in heroin-dependent patients. Long-term opioid dependence seems to impair prefrontal cerebral blood flow in particular [23]. Pezawas et al. [22] found an association between frontal volume loss and short-lasting abstinence. A change in the pattern of the anterior cingulate region has also been found to be associated with drug use [4].

Poor self-control could relate to one's resistance to the substance being abused, and hence perpetuate further drug

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use and relapse [9]. This study was conducted to examine the difference in neural activities associated with cognitive regulation between the heroin addicts and healthy volunteers. This study was conducted in China, which provides a fertile site for research on heroin addiction since addicts in China tend to be mono-drug users and since heroin is the most popular drug among them.

Formal approval to conduct this study has been obtained from the Ningbo Addiction Research and Treatment Centre (NARTC), Ningbo, China. Twenty-one Chinese men participated in this study. This study was conducted in accordance with the Declaration of Helsinki. The purpose of the study was explained to each of the participants and their informed written consent was obtained.

Eleven of the 21 participants were heroin-dependent patients newly admitted to the NARTC. These 11 participants were not concurrently abusing other drugs. The other 10 participants were healthy volunteers, matched in terms of age and general intelligence (as estimated by the Raven Progressive Matrix), who were recruited from the local community. All participants were right-handed, as screened by the Lateral Dominance Test [26], and had normal or corrected-to-normal vision. Furthermore, except for heroin dependence, all the participants in the patient group had no known history of head trauma or other medical/psychiatric conditions that could cause cognitive impairment. The respective mean ages of the patient and control groups were 29.54 (S.D. = 6.73) and 29.05 (S.D. = 5.62) years. The patient group had a mean history of 39.5 (S.D. = 20.8) months of heroin use and their mean dosage per day was 1.0 g (S.D. = 0.6). On the day of testing, all 11 heroin-addicted patients took heroin (the duration between the last heroin intake and scanning ranged from 3 to 7 h). At the time of scanning, no patient exhibited any symptoms of heroin withdrawal.

We developed an experimental measure, called the Arrow task, which is a simpler and culturally neutral variant of the spatial-congruence task (e.g. [21]), requiring the subject to read the direction of arrowheads as either “up” or “down”. The arrowheads were black in color and projected onto a white background. The size of each arrowhead was 2.6 cm × 6 cm. There were two conditions in this task: the Go and the Reverse conditions. During the Go condition, the subject was required to identify the correct direction of the arrowheads. This was followed by the Reverse condition, in which the subject was first required to identify the correct direction of the arrowheads and then give the opposite answers such that an “up” arrow should elicit a “down” response, and vice versa.

During scanning, the participant was required to press the response pad with the right thumb for the up but not the down responses. In other words, during the Go condition, the participants were required to respond to the up arrows. However, for the Reverse condition, the participants should not respond to the up arrows (see Fig. 1).

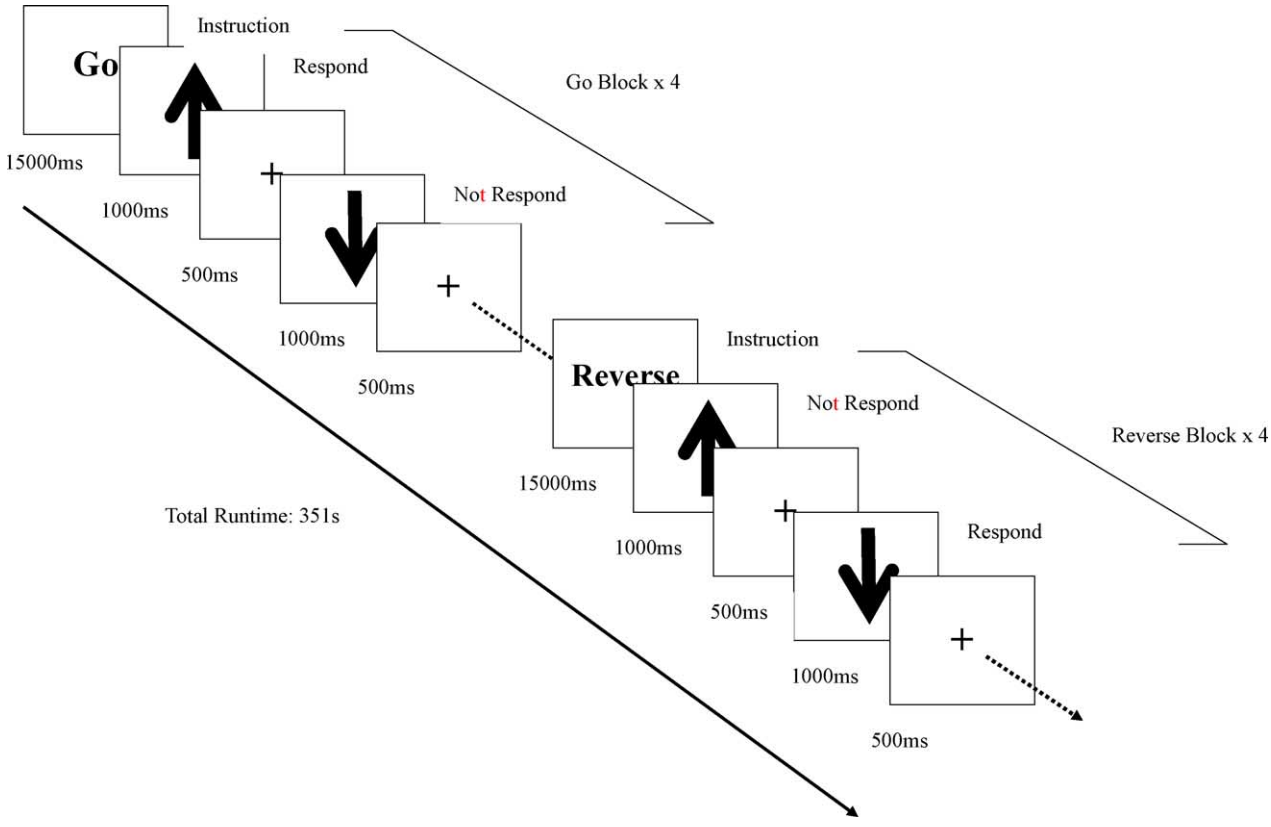

Fig. 1. Schematic representation of the experimental paradigm. ‘Go’ and ‘Reverse’ are English translation of Chinese instruction.

Each of the two task conditions was presented as four 27 s blocks, interleaved with a 15 s baseline. Each stimulus was shown for 1000 ms, followed by a 500 ms crosshair fixation, resulting in a total number of 18 trials in each block. The total runtime for the paradigm was 351 s. Prior to scanning, each participant was fully briefed and trained in the task. All the responses and respective reaction times were recorded via a response box. In the post-scanning debriefing, all the participants reported that they had remembered and complied with the instructions given during the training session.

All scanning was performed by a 1.5 T Siemens Sonata scanner. Fast Spin Echo high-resolution T1 images in the transverse direction (TR = 500 ms, TE = 7.7 ms, Matrix = 256 × 256, FOV = 220 mm × 220 mm, 25 slices, 4 mm thickness with 1 mm inter-slice gap) were obtained for structural information covering the whole brain. Functional images were acquired by Echo Planer Imaging sequence in the identical position to the T1 images (TR = 3000 ms, TE = 60 ms, Matrix = 64 × 64, FOV = 220 mm × 220 mm, 25 slices, 4 mm thickness with 1 mm inter-slice gap). A total number of 117 images were obtained for each participant.

The response times (RTs) in both the Go and the Reverse conditions were computed for both groups and differences were tested by repeated measure ANOVA. Furthermore, the errors committed in the Go and the Reverse conditions were compared by ANOVA.

Image analysis was conducted with *SPM2* (Wellcome Department of Cognitive Neurology, London) [10]. After the initial processing, in the regressor construction for the multiple regression, each block was modeled with a square-waved epoch and convolved with the canonical hemodynamic response function in SPM. Two regressors were constructed, one for the Go blocks and the other for the Reverse blocks. The rest periods were modeled implicitly as the baseline. 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, a linear contrast, Reverse versus Go, was constructed and subject-specific estimates of the contrast were obtained. The contrast estimates were entered into a standard SPM second-level analysis with the subject treated as a random effect, using a one-sampled *t*-test (d.f. = 9 and 10 for the control and the patient groups respectively). The expected mean difference value for the *t*-tests was set to zero. A voxel-wise intensity threshold ($p < 0.05$) and a spatial extent threshold (cluster size greater than 16 voxels) were combined to control for multiple comparisons (e.g. [24]) in the generation of the *t*-maps. Two sets of *t*-maps were generated, one for the control group and the other for the patient group. The regions thus identified should be involved in the response regulation in the arrow task; that is, in overcoming a habitual response pattern to adapt to novel task demands. Post hoc comparisons were also conducted to examine how the fMRI activity associated with response regulation (Reverse condition minus Go condition) differs statistically between the control and the patient groups in each of the activated regions found. One-tailed *t*-tests were used because a highly activated region for one group (e.g. the control group) should a priori have greater activity than the corresponding region in the other group (e.g. the patient group). All coordinates reported were in Talairach space converted from MNI space based on an algorithm given at http://www.mrccbu.cam.ac.uk/Imaging/mnispace.html. The percentage of the signal change was calculated by averaging the BOLD signal from all voxels in each identified region of activation, separated for different conditions and relative to the resting baseline.

To better understand the behavioral presentation of the patients and the normal controls on the experimental task, we administered the experimental task to a larger sample of 46 Chinese men, consisting of 25 heroin addicts (mean age = 28 years), who were drawn from the same clinical population as the patients who were scanned, and 21 normal controls (mean age = 29 years). These two groups were matched in terms of age and general intellectual ability ($p > 0.05$) as estimated by the Raven Standard Progressive Matrix [26].

The RTs (in ms, mean ± S.D.) and the mean errors committed for each condition are shown in Table 1.

The results of the repeated measure ANOVA revealed no significant main effect ($p = 0.119$) but a significant interaction effect between group and task performance ($F(1, 44) = 4.231$, $p = 0.046$). The performance of the two groups indicated that the normal controls took a longer time to complete the Reverse condition than the Go condition of the task, but for the patients, the reverse was true, as they took a shorter time to complete the Reverse condition than the Go condition.

The number of errors committed in the Go and the Reverse conditions was small. The patients tended to commit more errors than the normal controls, though the differences between the two groups were not significant ($p > 0.05$).

As shown in Fig. 2, for the control group, several brain regions showed statistically greater activation for the Reverse condition than for the Go condition, including two ventral lateral frontal regions (BA44 and 45), a left anterior cingulate region (BA32), and a left parietal region (BA39). For the patient group, frontal activation was minimal, with there being only a small cluster in the middle frontal gyrus (BA8). The major activations were located in the posterior part of the brain, including a left and a right parietal activation in the angular gyrus (BA39), and an inferior temporal region (BA21) (not shown in Fig. 2). No regions were more activated for

Table 1
Mean latency to response in response times and errors committed during the performance of the Go and Reverse conditions of the experimental task

	Heroin group ($n = 25$)		Control group ($n = 21$)	
	Go	Reverse	Go	Reverse
Response time (ms ± S.D.)	463 ± 60	459 ± 58	453 ± 83	487 ± 103
Mean errors (S.D.)	3.12 (0.80)	4.64 (2.34)	2.86 (1.17)	1.81 (1.25)

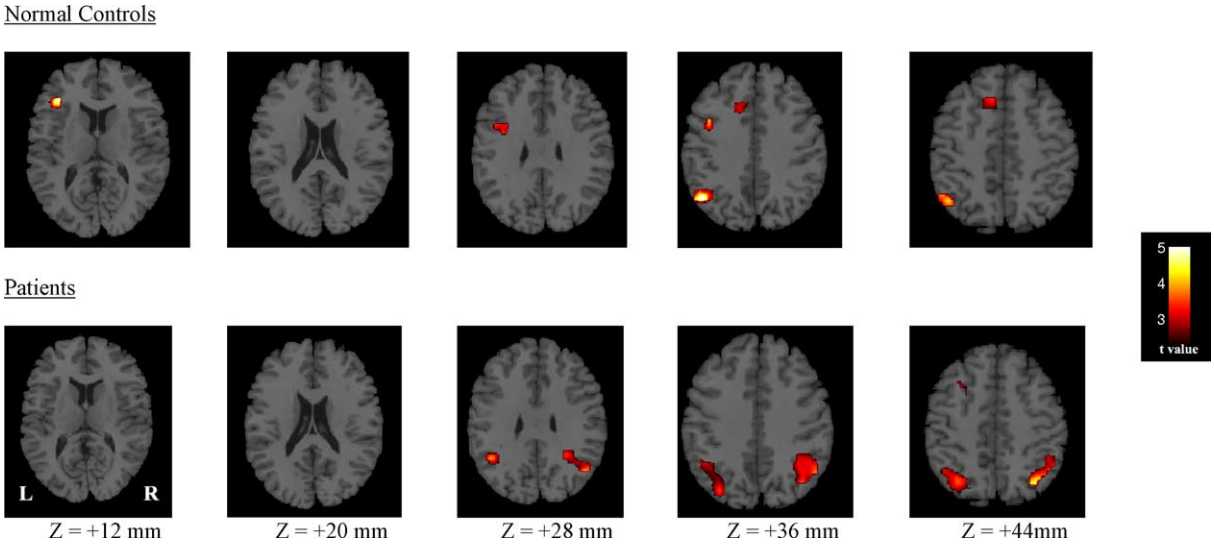

Fig. 2. Axial *t*-maps of brain activation ($p < 0.05$, minimum 16 contiguous voxels) for the Reverse vs. Go comparison for the control group (top panel) and the patient group (bottom panel). The images were superimposed on a standard SPM anatomical template brain in neurological convention with the *z* coordinates for each slice shown in Talairach space.

the Go condition than for the Reverse condition for either of the two participant groups. Summary information for these activations is provided in Table 2.

Table 3 shows the results from the post hoc comparisons for the percentage of signal change across the two participant groups. Among the regions identified for the control group, here called ROIs (regions of interest), the anterior cingulate cortex and the left inferior frontal gyrus at BA45 ROIs showed significant differences in activity between the two groups, but the left angular gyrus and the left inferior frontal gyrus region at BA44 ROIs did not. That is, activity in the anterior cingulate and the frontal BA45 was significantly greater for the control group than for the patient group. Among the ROIs identified for the patient group, the right angular gyrus showed significantly stronger activity for the patient group than for the control group.

Significant activations in the ventrolateral prefrontal region (VLPFC), the anterior cingulate gyrus, and the inferior parietal region on the left side were observed for the normal controls. These findings were consistent with previous inhibition studies that showed that structures for inhibition and error detection for such cognitive regulation include the middle frontal (BA9), precentral (BA6), inferior frontal (BA 44), cingulate (BA 24/32), and parietal structures (BA 40/39/7) (e.g.[1,11]).

We observed that the pattern of behavioral presentation as well as neural activation associated with cognitive regulation was indeed different between the heroin addicts and healthy controls. For the heroin addicts, they took a much shorter time to complete the more demanding, reverse condition of the task but committed more errors than the normal controls. This pattern of behavior, characteristic of people who are disinhibited and who tend to be impulsive, was consistent with previous reports of impulsivity observed in people who have abused heroin. For neural activation, significant activation of the left dorsolateral cortex instead of the ventrolateral prefrontal cortex, of the bilateral inferior parietal instead of just the left parietal, and of the left middle temporal regions were observed when they performed the same task. Furthermore, activity of the ACC was significantly attenuated. Since the patients participated in this study were carefully screened for the exclusion of any existing comorbid conditions that might confound cognitive function, the observed change in neural activity associated with cognitive regulation in the heroin

Table 2
Summary information for activated regions shown in Fig. 2

Participant group	Anatomical structure	Brodmann's areas	Stereotaxic coordinates			Peak *z* score	Volume (voxel)
Control	Left angular gyrus	39	−46	−58	41	3.86	59
	Left anterior cingulate cortex	32	−9	24	36	2.70	42
	Left inferior frontal gyrus	44	−37	5	27	3.13	41
	Left inferior frontal gyrus	45	−40	28	10	3.62	25
Patient	Left angular gyrus	39	−41	−48	29	3.80	48
	Right angular gyrus	39	50	−51	39	3.30	45
	Left inferior temporal gyrus	21	−54	−46	−2	3.68	22
	Left middle frontal gyrus	8	−25	17	45	3.00	16

Table 3
t-tests on percentage of signal change for the two sets of ROIs shown in Fig. 2

	ROIs	Percent of signal change		*p* value
		Control	Patient	
Normal controls	Left angular gyrus	0.32 (0.07)	0.33 (0.17)	0.52
	Left anterior cingulate cortex	0.24 (0.07)	0.07 (0.07)	0.05*
	Left inferior frontal gyrus	0.25 (0.06)	0.18 (0.08)	0.25
	Left inferior frontal gyrus	0.31 (0.04)	0.10 (0.09)	0.04*
Patients	Left angular gyrus	0.15 (0.09)	0.26 (0.07)	0.15
	Right angular gyrus	0.09 (0.12)	0.35 (0.09)	0.05*
	Left inferior temporal gyrus	0.07 (0.09)	0.23 (0.05)	0.06
	Left middle frontal gyrus	0.19 (0.06)	0.27 (0.07)	0.21

* Significant at $p \leq 0.05$.

addicts who participated in this study could not, therefore, be explained by any comorbid psychiatric or neurological conditions.

The VLPFC is linked strongly with the orbital PFC through its thalamo-hypothalamic connections, and the OPFC in turn is a station within the frontostriatal circuit that has strong connections to the amygdala and other parts of the limbic system. Therefore, the VLPFC and the OPFC may play key roles in the motivational systems necessary for optimal performance on tasks [12], decision-making (e.g. [13]), and comprehension of abstract reinforcers [25]. The attenuated activity of the VLPFC in the patients may suggest that the endogenous and volitional control of their behavior is compromised. Consequently, their behavior may be disproportionately determined by environmental contingencies, environmental cues (e.g. drug-craving cues), and automatized or habitual behaviors. The effect of this would be to compound the maintenance of drug abuse: if chronic heroin users are especially influenced by environmental contingencies and cues, then an inhibitory dysfunction may reduce their capacity to inhibit these external influences.

Bunge et al. [2] compared cognitive control between 8- to 12-year-old children and healthy young adults and found that immaturity in cognitive control was associated with an inability to recruit PFC regions observed in the fully developed brains of healthy young adults. They further observed that the activation of posterior association areas was a stronger determinant of the level of performance in cognitive regulation in children than were prefrontal regions: better performers exhibited bilateral inferior parietal activation. In view of Bunge et al.'s study, could the recruitment of additional activity of the right inferior parietal region observed in the heroin addicts be related to possible enhancement of the efficiency of cognitive regulation, which could have been compromised as a result of the attenuated prefrontal activity? Future research is required for verification of this important theoretical question.

Activation of the left prefrontal-SMG network has been preferentially observed during verbal working memory tasks (e.g. [19,28]). Recent neuroimaging studies (e.g. [28]) have demonstrated strong involvement of both the left SMG and the DLPFC (BA44/45/9) in this loop [7]. Martin et al. [19] suggested that a left inferior and mid-frontal region and a left SMG creates a network for phonological short-term memory. Could the shift in the pattern of neural activation, especially in the prefrontal–parietal regions observed also affect the working memory of the heroin addicts? Finn et al. [8] report that working memory limitations such as low working memory capacity can exacerbate the poorer impulse control that was observed in people consuming alcohol excessively.

Attenuated activity of the anterior cingulate region observed in the heroin-dependent patients was consistent with previous reports. Forman et al. [9] studied the activation of the anterior cingulate cortex of opiate addicts during the occurrence of false alarms. They observed an attenuated anterior cingulate cortex error signals as well as significantly poorer task performance among opiate addicts relative to healthy volunteers. Kaufman et al. [14] report that the anterior cingulate, critical for cognitive control, is less responsive in chronic cocaine users. Other researchers have also observed error-related activations in both the ACC and the left prefrontal cortex in other clinical populations (e.g. [14,16]). It is plausible that, despite differences in pathologies, a common dysfunction in cognitive regulation of impulsive behavior might be shared. This speculation awaits verification in future research. Furthermore, we speculated that the hypoactivity of the heroin users may relate to an inefficient self-monitoring cognitive regulation system for adaptive behavioral output. As Kaufman et al. [14] have suggested, reduced inhibitory control, diminished action monitoring, and diminished responsivity to one's errors associated with drug users appear to be consistent with the pathological drug-use pattern and serve to prolong the maintenance of drug abuse.

Previous studies have demonstrated that the neural activity of substance abusers could be enhanced by drug-related stimuli. Daglish et al. [4] suggest that drug-dependence circuitry is perhaps related to a greater degree of activation of regions associated with processing the autobiographical stimuli accompanying drug use. Effective intervention should, therefore, focus on de-conditioning the sensitized circuits and normalizing neural activity for proper cognitive function.

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