Published in final edited form as:

Behav Brain Res. 2011 January 20; 216(2): 639–646. doi:10.1016/j.bbr.2010.09.004.

Identification of Hyperactive Intrinsic Amygdala Network Connectivity Associated with Impulsivity in Abstinent Heroin Addicts

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Abstract

Impulsivity is a pathological hallmark of drug addiction. However, little is known about the neuropsychological underpinnings of this impaired impulsive control network on drug addiction. Twenty two abstinent heroin dependent (HD) subjects and fifteen cognitively normal (CN) subjects participated in this study. Resting-state functional connectivity MRI was employed to measure abnormalities in the intrinsic amygdala functional connectivity (iAFC) network activity and the Barratt Impulsive Scale, 11th version was used to measure impulsivity. Linear regression analysis was applied to detect the neural constructs underlying impulsivity by correlating iAFC network activity with impulsive scores. In the HD group, higher impulsivity scores and significantly enhanced iAFC network activity were found, especially in bilateral thalamus, right insula, and inferior frontal gyrus. Markedly decreased anticorrelated iAFC network activity was seen in the left precuneus, and even switched to positive correlation pattern in right precuneus, relative to the CN group. The iAFC network strengths in the HD group were positively correlated with impulsivity in the right subcallosal gyrus, insula, thalamus and posterior cingulate cortex, and negatively correlated in left fusiform area. In the CN group, the left pre-somamotor area-amygdala connectivity was positively correlated, and right orbital frontal cortex-amygdala and precuneus-amygdala connectivity were negatively correlated with impulsivity scores. Our study demonstrates

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Financial Conflict of Interest: No authors of this paper have reported any possible conflict of interests.

different constructs of the impulsive network in HD and CN subjects. Altered iAFC network connectivity in HD subjects may contribute to the loss of impulsive control. This further facilitates our understanding of the neural underpinnings of behavior dysfunction in addiction.

Keywords

Heroin dependent; impulsivity; functional connectivity MRI; amygdala network

1. Introduction

Impulsivity is a pathological hallmark of drug addiction and is primarily thought to arise as a result of impaired inhibitory control [17, 18, 32, 34]. Recently, neuroimaging techniques have been widely employed to investigate the neural mechanisms of impulsivity and a set of neural correlates of impulsivity have been identified. These include the ventromedial prefrontal cortex, anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), and subcortical regions, including the amygdala, ventral tegmental area, and nucleus accumbens [2, 14, 19, 23, 37]. Specifically, previous fMRI task-specific studies have demonstrated that significantly lower ability of poor impulse control and impaired response inhibition in performing the response suppressing task in the chronic heroin users and abstinent alcohol-dependent subjects [1, 8]. For example, during a Go/NOGO task, abstinent heroin-dependent patients showed hypoactivity in medial prefrontal cortex and ACC relative to healthy, drug-naïve participants [8, 19], suggesting a sustained negative effect of heroin on the areas involved in executive control function in abstinent addicts. Moreover, it was clearly demonstrated that hypoactivity in the prefrontal cortex, which often operates in control function, and hyperactivity in the impulse system during cue-induced craving in heroin users. These significantly imbalanced neural activities in two interacting, but distinct, neural circuits suggest that the control system was probably hijacked by the impulsive system under the craving state [2, 37]. Although these studies provide important information regarding the brain's structure and functional localization associated with impulsivity, little is known about the behavioral significance of the interconnections among these spatially remote, but functionally localized brain regions using conventional volumetric and functional MRI methods.

It is well-established that the high-order cognitive behavior is determined by the neurocognitive network with a high-degree connectivity pattern among discrete brain regions [25, 28]. Thus, it is necessary to investigate the connectivity pattern of specific regions which can reflect the impulsive system to understand the neural mechanisms of impulsivity. On the one hand, advances in resting-state functional connectivity MRI (R-fMRI) techniques provide a powerful tool to study the construction of the intrinsic, interconnected neural networks and their relation to cognitive or behavioral states in human and non-human primates [4, 35]. Moreover, abnormal pattern in resting-state functional connectivity network in patients with Alzheimer's disease, major depression, generalized anxiety disorder, as well as nicotine addiction have been identified [6, 9, 12, 20]. On the other hand, it is widely accepted that the amygdala, as a hub, is central to the regulation and integration of information processing under cue-elicited drug craving, and is also a crucial

component of the impulsivity system, which preferentially responds to small, immediate reward over large, delayed reward [2]. These findings suggest that the detailed, intrinsic amygdala functional connectivity (*iAFC*) network associated with impulsive systems may characterize the behavioral phenotype of impulsive control and provide additional evidence for the neural mechanisms underlying addiction.

Recently, it was reported that a disrupted *iAFC* network was found in abstinent heroin users using a R-fMRI approach [21, 22, 33, 38]. These studies suggested that this altered amygdala functional connectivity among brain regions might contribute to the loss of control and impaired inhibitory behaviors, but failed to find direct evidence can reveal the neural substrates of impulsivity. Collectively, these findings lead us to propose the neural network-based hypothesis that the dysfunctional *iAFC* network is due to chronic exposure to heroin and also should be associated with impaired impulsive control behavior, even under the abstinent state.

In the present study, therefore, we test the hypothesis that 1) The altered *iAFC* network pattern is associated with impulsive behavior, as measured by the Barratt Impulsiveness Scale (BIS, version 11) [27]; 2) The constructs of the impulsivity-associated network in abstinent heroin dependent (HD) subjects are different in comparison with those of cognitively normal (CN) subjects.

2. Materials and Methods

2.1 Participants

30 abstinent heroin-dependent subjects and 20 healthy volunteers who never used opiates were recruited from Beijing Ankang Hospital (Beijing, China) and the surrounding suburban areas in this study. The experimental procedure was approved by the Beijing Ankang Hospital and the Beijing Institute of Basic Medical Science and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all subjects prior to scan. 8 heroin subjects and 5 healthy subjects were excluded from this study due to motion artifacts (i.e. exceeding more than 1 mm translational movement or more than 1° rotational movement) leaving 22 abstinent heroin subjects and 15 control subjects for the final data analysis.

All participants were male, right-handed and well-matched for age and years of education. Inclusion and exclusion criteria for heroin abusers and control subjects were described previously [8]. Briefly, heroin subjects met DSM-IV criteria for heroin dependence, were abstinent for at least 4 weeks, tested negative for morphine in urine-analysis and human HIV in blood test, had used heroin for at least 2 years, and had normal intelligence. None of the subjects had a history of neurological and psychiatric disease, seizures, head injury and abnormalities demonstrated by an anatomical MRI. Structured interviews by two psychiatrists were conducted with each participant before admission in the study.

2.2 Psychological Instrument

Impulsivity was assessed by self-report instruments of the BIS-11 (Chinese revised edition), which contains 30 4-point Likert-type items [27]. Higher scores signify higher impulsivity. All participants completed the questionnaire and the results are presented in Table 1.

2.3 MRI Acquisition

Imaging was performed using a whole-body 3T Signa GE scanner with a standard transmit-receive head coil. During the resting-state acquisitions, the study participants were instructed to close their eyes and relax. Axial resting-state fMRI datasets of the whole brain were obtained in 6 minutes with a single-shot gradient echo-echo planar imaging (EPI) pulse sequence. The fMRI imaging parameters were: TE = 25 ms, TR = 2 s, flip angle = 90°, 20 slices, slice thickness = 5 mm, space = 1 mm, matrix size 64×64 and field of view 24×24 cm. High resolution spoiled gradient-recalled echo (SPGR) 3D axial images were acquired for anatomical reference. The parameters were: TE/TR of 4.8/10.4 ms, flip angle = 15°, 140 slices, slice thickness = 1 mm, matrix size of 256×256, and field of view 24×24 cm.

2.4 fMRI data preprocessing

All image data preprocessing and analysis were conducted with Analysis of Functional NeuroImages software (AFNI, <http://afni.nimh.nih.gov/afni/>), Statistical Parametric Mapping (SPM8, <http://www.fil.ion.ucl.ac.uk/spm/software/spm8/>), and Matlab software (Matlab 7.0, MathWorks, Natick, MA, <http://www.mathworks.com/>). For the preprocessing of fMRI images, the first 5 data points of resting-state datasets were discarded in order to eliminate the magnetization nonequilibrium and obtain a stable state. This was followed by physiological motion correction, volume registration, and motion correction. Possible contamination from the signals existing in white matter, cerebrospinal fluid, and six motion vectors were regressed out. A band-pass filter was then applied to keep only low frequency fluctuations between 0.015 Hz and 0.1 Hz.

2.5 Intrinsic amygdala functional connectivity network

Firstly, the left and right amygdalae were drawn manually on T1-weighted 3D SPGR images, according to the literature [11, 31]. The specific procedures used to locate the amygdala region and select the amygdala voxels from the EPI dataset are described below.

The most posterior boundary of the amygdala adjoins the anterior alveus of the hippocampus and the temporal horn of the lateral ventricle in the sagittal plane. The anterior boundary follows the natural boundaries of the gray matter in the anterior direction in the axial plane. The superior and the inferior boundaries were defined coronally as the ventral horn of the subarachnoid space and the most dorsal finger of the white-matter tract under the horn of the subarachnoid space, respectively. The lateral and the mesial boundaries were defined coronally at 2 mm from the surrounding white matter and from the subarachnoid space, respectively. A mouse-controlled cursor traced relevant coronal, sagittal, and axial slices. Boundaries were displayed in real time on these orthogonal MRI slices with AFNI software. The same coordinates in SPGR and functional EPI images were determined, and amygdala masks were applied to the latter. The time course of the amygdala was extracted from the functional EPI images. The spatial resolutions in SPGR (1.0-mm) and EPI images (3.75

mm) were different, therefore, only those voxels in EPI images that contained at least 50% of amygdala voxels masked on the 3D SPGR images were included in the voxel time course analysis [31].

Then, the averaged time course within the amygdala mask, as the seed time course, was correlated to the time courses of all brain voxels using Pearson cross-correlation. Next, we applied the Pearson correlation coefficients (r) to a Fisher's z Transform Analysis, which yielded variants of approximately normal distribution [$m = 0.5\ln(1+r)/(1-r)$] [39]. Finally, the data was spatially normalized to the Talairach template image, resampled to 2mm isotropic voxels, and smoothed with a Gaussian kernel (6mm FWHM) using AFNI software.

2.6 Statistical analysis

2.6.1 Behavioral data—The statistical analyses were conducted with SPSS 16.0 software (SPSS Inc., Chicago, IL, USA). An independent-sample t -test was employed to analyze the difference between demographic data and BIS- 11 scores for group comparison. The results were considered significant at $p < 0.05$. The data was presented as mean $\pm$ standard deviation.

2.6.2 Participant-level analysis for the iAFC network patterns—After obtaining the *iAFC* map for each individual subject, the individual *iAFC* maps were grouped together for the CN and heroin groups. The *iAFC* network for each group was generated by applying a voxelwise one sample t -test within each group of subjects against a null hypothesis of no connectivity ($p < 0.01$, corrected for multiple comparisons with AlphaSim program).

2.6.3 Group-level analysis for the iAFC network pattern—To find group differences, we selected 30 regions of interest (ROIs) based on our findings and previous neuroimaging studies of patients with heroin addiction that have revealed abnormal functions in regions associated with cue-induced craving processing [21, 22, 37, 38]. These areas include bilateral medial frontal cortex (MeFG), OFC, dorsolateral prefrontal cortex (DLPFC), middle frontal cortex, inferior frontal gyrus (IFG), middle temporal cortex (MTG), posterior cingulate cortex (PCC), inferior parietal cortex (IPC), precuneus, insula, hippocampus, thalamus, caudate, and putamen. Distinctive ROI in our data falling within the *iAFC* network were comprised of 4mm-radius spheres and centered on the public foci [21, 22, 37]. Then, the averaged m values of all voxels in each ROI were extracted from the individual *iAFC* map and the strength of changes in the *iAFC* network was quantitatively analyzed using SPSS16.0. A two-sample t -test and a small volume correction analysis were performed with the statistical threshold $p < 0.05$.

2.6.4 Behavioral significance of the iAFC network—To determine the behavioral significance of the *iAFC* network alteration, a linear regression analysis was conducted between the voxelwise *iAFC* strength (m value) and the BIS total scores in the heroin subjects and the CN subjects separately.

3. Results

3.1 Subject characterization

Demographic information and clinical evaluations are shown in **Table 1**. No significant difference in age and education was noted between HD and CN groups. BIS-11 total scores in HD group were significantly higher than those in the CN group ($p < 0.05$).

3.2 The iAFC network patterns for CN group and heroin group

The functional pattern of the *iAFC* network for CN group was observed in the prefrontal and limbic systems. The positive *iAFC* network included the regions of bilateral amygdala, MTG (BA21), right OFC (BA25), superior temporal gyrus (STG, BA38), and ACC (BA32). The anticorrelated *iAFC* network (negative correlation) includes the regions of bilateral precuneus (BA7), IPC (BA40), MeFG (BA10), DLPFC (BA9,46), IFG (BA44), right fusiform area (FFA, BA19), left lingual gyrus (BA19) and cerebellum. These results are described in **Figure 1**(left) and **Appendices A**. Similarly, *iAFC* network pattern for the HD group has increased positive correlation with the amygdala, especially in the regions of the temporal system and subcortical regions, including the bilateral OFC, caudate, lentiform nucleus, thalamus, insula (BA13), STG (BA38), MTG(BA21), FFA(BA37), posterior cingulate cortex (PCC, BA23), and lingual gyrus; and enhanced anticorrelation with the amygdala, especially in the prefrontal system, parietal system, and occipital system, including the regions of bilateral IPC (BA40), DLPFC (BA9,46), MeFG (BA10), IFG(BA45/47), as shown in **Figure 1**(right) and **Appendices B**.

3.3 Difference of the iAFC network pattern between HD and CN groups

Based on the group t-test comparison between the heroin users and control subjects, a significant alternation of the *iAFC* network was observed in several brain regions. The positive *iAFC* network was significantly enhanced in the bilateral thalamus and right insula (BA13). The anticorrelated *iAFC* network was significantly increased in the right IFG, and significantly decreased in the left precuneus (BA7). In addition the correlation changed from negative to positive in the right precuneus (BA7), as illustrated in **Figure 2**.

3.4 Correlation of the iAFC network with impulsivity scores

Statistical maps of the linear regression analysis between *iAFC* network strength (m value) and BIS-11 total scores for impulsivity in the heroin group showed positive correlations in the right subcallosal gyrus (BA25/11), insula (BA13), PCC (BA29) and thalamus. Negative correlations were seen in the left FFA (BA37). No significant correlations in these regions were found in comparison subjects, as illustrated in **Figure 3** and **Table 2** (whole brain correction with AlphaSim, $p < 0.01$, cluster size $> 1180 \text{ mm}^3$). The scatter plots in **Figure 3** further characterize the quantitative information in the five regions where the *iAFC* network activity was linearly correlated with impulsiveness scores.

Comparison subjects showed a strong positive correlation between *iAFC* network strength and BIS total scores in the left presomamotor area (pre-SMA, BA6). A negative correlation was seen in the right OFC (BA11) and right precuneus (BA7). No significant correlation in

these regions was seen in the heroin subjects, as described in **Figure 4** and **Table 2** (whole brain correction with AlphaSim, $p < 0.01$, cluster size $> 1180 \text{ mm}^3$).

4. Discussion

In the current study, we demonstrated the network-based hypothesis that the sustained, hyperactive *iAFC* network in abstinent HD subjects was associated with high impulsivity. Further, the impulsivity-related regions within the *iAFC* network were different between abstinent HD subjects and CN subjects. These rewired constructs of *iAFC* network suggest that the hyperconnection of the *iAFC* network may play a fundamental role in the high impulsivity in abstinent heroin addicts.

4.1 Altered *iAFC* network pattern for HD group compared to CN group

In the amygdala connectivity map, the brain regions within the positive *iAFC* network are largely located in the limbic and striatum systems, and include the bilateral caudate, putamen, nucleus accumbens, and other subcortical regions. Brain regions within the anticorrelated *iAFC* network are oriented in the prefrontal and parietal-occipital systems, as illustrated in **Figure 1**. This pattern of the *iAFC* network during the resting condition is consistent with other studies [6, 30, 31]. Moreover, there is a significant increase in *iAFC* network strength in both the positive and anticorrelated *iAFC* networks in HD subjects, especially in the bilateral thalamus, right insula and IFG. Similarly, a remarkably reduced anticorrelated *iAFC* network in the HD subjects was found in the left precuneus, and a switch from a negative to positive correlation pattern was seen in the right precuneus, as illustrated in **Figure 2**. These regions with altered connectivities to amygdala in abstinent HD subjects were involved in drug-induced craving, reward, and response inhibition [7, 8, 16, 26]. In addition, dysfunctional connectivity in chronic heroin users was reported in the prefrontal cortex, ACC, ventral striatum, insula, and amygdala by employing a graph theory analysis method. This disconnection may contribute to the reduced self-control, impaired inhibitory function, and deficits in stress regulation in chronic heroin users [21]. More recently, abnormal functional connectivity, including amygdala-OFC connection in chronic heroin users with methadone treatment was identified and supports the view that dissociated functional connectivity is related to weakened cognitive control in the addictive state [22]. Taken together, this altered *iAFC* network pattern suggests that a functional rewiring of brain networks exists in abstinent heroin users.

4.2 Enhanced *iAFC* network activity is correlated with impulsivity

Unlike task-dependent fMRI studies where brain responses are dependent on specific cognitive tasks, R-fMRI studies can identify the constructs of brain networks where the changes in distributed network connectivity are associated with behavioral states under task-free conditions. In the current study, we performed a linear regression analysis that combined impulsiveness scores with *iAFC* network strength and identified the construct of impulsivity at the system level. Specifically, the positively correlated regions included the right subcallosal gyrus, insula, thalamus and PCC in the HD group, and the left pre-SMA in control group subjects. This is illustrated in **Figure 3 A-D** and **Figure 4 A**. It indicates that

the stronger the connectivity between these regions with the amygdala, the higher the impulsiveness scores, and the lower the impulsive control.

Converging evidence from neuroimaging studies has shown that these regions form part of a system representing internal state-modulated behavior, including fear-memory, self-related mental representations, negative feedback processing, and also are critical for efficient execution of the corresponding actions [5, 13, 36]. In addition, it has also been suggested that these regions are involved in steep time discounting or value discounting regulation, and are preferentially activated by making decisions involved in immediate action over delayed rewards. This can reflect impulsive behavior [10, 24, 29]. Moreover, this value discounting reward can be simultaneously reduced by episodic future thinking [29]. Collectively, these studies consistently support the view that the functional integration of the impulsivity-related network constituted by above noted regions is associated with internal state regulation.

Interestingly, we also found the negatively correlated brain regions of the impulsivity-associated *iAFC* network including the left FFA in the HD group, and right OFC and precuneus in the control group, as illustrated in **Figure 3 E** and **Figure 4 B** and **C**. This indicates that the higher the impulsivity, the weaker the connection strength of these regions to the amygdala. These results suggest the function of these negatively correlated regions may be suppressed when the subject chooses immediate over delayed long-term larger reward underlying the specific goal-directed behavior. In short, these regions represent the subcomponents within the *iAFC* network correlated with impulsivity and also highlight the critical contribution to the impulsive behavior at the system level that may increase the risk for addiction.

In addition, we have found a different construct of impulsivity-associated networks in abstinent HD subjects and CN subjects. Our finding is consistent with a recent report that the activated BOLD signal was negatively correlated with high impulsivity only in alcoholics but not in control subjects in the ventral striatum and anterior cingulate during gain anticipation elicited by a monetary incentive delay task [3]. This shifting impulsivity-associated network architecture and neurocircuitry in addicts may result from persistent neuronal changes and long-lasting neuroadaptation after exposure to drugs of abuse [15]. Therefore, it is reasonable to propose the neural mechanism of impulsivity in abstinent HD subjects on the network-based level: hyperconnection of *iAFC* network induced by the altered internal state activates the impulsivity-associated network activity, and leads addicted subjects with high impulsiveness to choose immediate, short reward actions despite a long-term negative consequence. This finding provides new insights into the neural mechanisms of drug addiction.

Our study is not without limitations. First, the self-report questionnaire may not have reported their inner impulsivity honestly. It is necessary to detect the neural correlates of the distinctive behavioral phenotype at the network level by combining the questionnaire with the specific, complex cognitive task associated with impulsive control. Second, we predefined the bilateral amygdala as a seed region and proved the behavioral significance of the *iAFC* network activity, which may not reflect the changes of the whole brain functional

network. Future studies are needed to investigate the functional role of the large-scale, distributed, functional neural network including whole-brain regions in addicts. Third, this is the cross-section of a larger study without drug treatment. Longitudinal studies with detoxification treatment are needed to evaluate the brain functional network alteration and might provide a new strategy for preventing addiction.

5. Conclusion

The findings of this study suggest that the observed hyperconnection of the *iAFC* network in abstinent heroin users make a critical contribution to higher impulsivity and represent the pathological damage that may underlie the neurobiological mechanism for addictive behavior – loss of impulsive control. This further facilitates our understanding of the neural underpinnings of behavioral dysfunction associated with addiction. It is also suggested that the network-based R-fMRI approach could be applied to evaluate the consequence of heroin abuse and the related alteration of brain circuitry at a system level.

Acknowledgment

Dr. Zhijun Zhang and Dr. Yang had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Dr. Xie and the other coauthors had full access to all the data in the study. The authors thank Dr. Gao-hong Wu for the data analysis, Mr. Douglas Ward for the statistical analysis.

This work was supported by National Natural Science Foundation of China (30825014, 30971016, ZJZ), Chinese Ministry of Science and Technology grants: 2003CB51540 (ZY), and China Scholarship Council CSC20070320 (CX).

Appendices

A. Intrinsic amygdala functional connectivity (*iAFC*) network pattern for control subjects

Brain region	Side	BA	Cluster Size (mm ³)	Talairach coordinates			z score
				x	y	z	
Positive <i>iAFC</i> network							
Amy/PHG	R		60368	25	1	−14	6.55
Amy/PHG	L			−18	−4	−14	6.30
OFC	R	25		13	13	−17	3.97
STG	R	38		40	15	−23	4.46
ACC	R	32		4	32	−6	3.86
MTG	L	21		−47	−4	−21	4.52
MTG	R	21		47	−1	−19	3.09
Anticorrelated <i>iAFC</i> network							
Precuneus	L	7	103360	−23	−63	38	−5.06
Precuneus	R	7		4	−71	42	−3.26
IPC	L	40		−35	−52	39	−4.08
MeFG	R	10		15	57	0	−3.50
MeFG	L	10		−8	61	2	−2.96
DLPFC	R	9,46		40	34	26	−3.98
DLPFC	L	9,46		−44	33	15	−3.62

Brain region	Side	BA	Cluster Size (mm ³)	Talairach coordinates			z score
				x	y	z	
IFG	L	44		-54	9	20	-3.92
IFG	R	44		53	9	22	-3.29
Lingual gyrus	L	19	3416	-10	-86	-14	-3.41
IPC	R	40	3136	47	-39	42	-3.85
FFA	R	19	1232	41	-75	-14	-3.11
Cerebellum	L		1792	-35	-63	-26	-3.22

Notes: The results were obtained with one sample *t*-test, $p < 0.01$, cluster size $> 1180 \text{ mm}^3$. Abbreviation: BA, Brodmann's area; x,y,z, coordinates of peak locations (highest z-values) in the Talairach space. R, right; L, left; Amy, amygdala; PHG, parahippocampus gyrus; OFC, orbital frontal cortex; STG, superior temporal gyrus; ACC, anterior cingulate cortex; MTG, middle temporal gyrus; IPC, inferior parietal cortex; MeFG, medial frontal gyrus; DLPFC, dorsolateral prefrontal cortex; IFG, inferior frontal gyrus; FFA, fusiform area.

B. Intrinsic amygdala functional connectivity (*iAFC*) network pattern for heroin subjects

Brain region	Side	BA	Cluster Size (mm ³)	Talairach coordinates (LPI)			z score
				x	y	z	
Positive <i>iAFC</i> network							
Amy/PHG	R		153424	25	−3	−18	7.19
Amy/PHG	L			−22	−5	−15	6.99
OFC	R	25		13	13	−17	5.47
OFC	L	11		−3	38	−13	4.68
Caudate	R			10	14	−2	3.62
Caudate	L			−7	11	−2	4.11
Thalamus	R			13	−20	6	4.48
Thalamus	L			−11	−25	7	4.30
Lentiform nucleus	R			23	0	−5	4.30
Lentiform Nucleus	L			−28	0	−2	4.62
Insula	R	13		46	−13	7	4.38
Insula	L	13		−35	−13	10	4.18
STG	R	38		34	17	−27	5.82
STG	L	38		−31	16	−23	4.99
MTG	R	21		47	−1	−19	4.50
MTG	L	21		−47	−4	−21	5.33
FFA	R	37		26	−50	−9	3.82
FFA	L	37		−27	−41	−14	4.36
PCC	R	23		6	−40	22	4.00
PCC	L	23		−3	−40	23	3.49
Lingual Gyrus	R	19		22	−61	2	5.20
Lingual Gyrus	L	18		−19	−55	2	4.18
Anticorrelated <i>iAFC</i> network							
IPC	L	40	212824	−45	−47	42	−5.15
IPC	R	40		47	−39	42	−4.88

Brain region	Side	BA	Cluster Size (mm ³)	Talairach coordinates (LPI)			z score
				x	y	z	
DLPFC	R	9,46		26	32	34	-4.45
DLPFC	L	9,46		-47	21	24	-4.27
MeFG	R	10		15	57	0	-4.88
MeFG	L	10		-8	61	2	-4.84
IFG	R	47		52	27	12	-4.17
IFG	L	45		-50	20	16	-4.51

Notes: The results were obtained with one sample *t*-test, $p < 0.01$, cluster size $> 1180 \text{ mm}^3$. Abbreviation: BA, Brodmann's area; x,y,z, coordinates of peak locations (highest z-values) in the Talairach space. R, right; L, left; Amy, amygdala; PHG, parahippocampus gyrus; OFC, orbital frontal cortex; STG, superior temporal gyrus; ACC, anterior cingulate cortex; MTG, middle temporal gyrus; FFA, fusiform area; PCC, posterior cingulate cortex; IPC, inferior parietal cortex; DLPFC, dorsolateral prefrontal cortex; MeFG, medial frontal gyrus; IFG, inferior frontal gyrus.

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Figure 1. The patterns of the iAFC network for CN group and HD group subjects

The results illustrated that more brain regions are involved in the iAFC network in the heroin group (right) compared to the control group (left), which are mainly located in the prefrontal system, the parietal-occipital system, temporal lobule and subcortical regions. Blue color is anticorrelation (negative), bright color is positive correlation. The pattern was produced by a one sample t-test ($p < 0.01$, corrected). The color bar is presented with z score. Top image: lateral view; Bottom image: medial view.

Figure 2. Significantly altered iAFC network in heroin group compared to control group

The results showed significantly decreased anticorrelation in the left precuneus (close to zero), significantly increased anticorrelation in the right inferior frontal gyrus and significantly increased correlation in the right insula and bilateral thalamus. A reversed correlation pattern in the iAFC network was also found in right precuneus. Significant level was set at: *, $p < 0.05$; **, $p < 0.01$. Error bars are presented with standard deviation. Abbreviation: Pcu, precuneus; IFG, inferior frontal gyrus; Ins, insula; Tha, thalamus.

Figure 3. Robust linear regression analysis between the *iAFC* strength and BIS total scores in distinct regions in HD group

The results showed a strong positive correlation between the *iAFC* network strength and the BIS total scores in the right subcallosal gyrus, insula, posterior cingulate cortex (PCC) and thalamus, and robust negative correlation in left fusiform area (FFA) in the HD group (red color), but not in CN group (blue color). **A)** right subcallosal gyrus: regression coefficient $r^2 = 0.22$, $p < 0.02$ (HD group), $r^2 = 0.06$, $p < 0.19$ (CN group); **B)** right PCC: $r^2 = 0.26$, $p < 0.01$ (HD group), $r^2 = 0.003$, $p < 0.95$ (CN group); **C)** right insula: $r^2 = 0.64$, $p < 4.42E-6$ (HD group), $r^2 = 0.10$, $p < 0.13$ (CN group); **D)** right thalamus (Tha): $r^2 = 0.33$, $p < 0.003$ (HD group), $r^2 = 0.06$, $p < 0.68$ (CN group); **E)** left FFA: $r^2 = 0.42$, $p < 1.43E-6$ (HD group), $r^2 = 0.06$, $p < 0.68$ (CN group). Each point represents one participant. Images and coordinates are in Talarach space.

Figure 4. Robust linear regression analysis between the *iAFC* strength and BIS total scores in distinct regions in CN group

The result showed a strong positive correlation between the *iAFC* network strength and the BIS total scores in the left pre-SMA, negative correlation in right OFC and right precuneus in the CN group (blue color), but not in the HD group (red color). **A)** left pre-SMA: regression coefficient $r^2 = 0.42$, $p < 0.005$ (CN group), $r^2 = 0.04$, $p < 0.7$ (HD group); **B)** right Precuneus: $r^2 = 0.66$, $p < 0.0001$ (CN group), $r^2 = 0.0001$, $p < 0.33$ (HD group); **C)** right OFC: $r^2 = 0.57$, $p < 0.0007$ (CN group), $r^2 = 0.01$, $p < 0.38$ (HD group). Each point represents one participant. Images and coordinates are in the Talaraich space.

Table 1

Demographic information and behavioral performance

	HD (n=22)		CN (n=15)		P
	Mean	SD	Mean	SD	
Age (year)	33.05	6.04	28.91	7.82	0.06
Education (years)	10.86	2.40	9.83	2.94	0.26
Duration of heroin use (years)	6.59	3.72	-	-	-
Dosage of heroin use (g/day)	0.96	1.26	-	-	-
Duration of abstinence from heroin (weeks)	8.05	2.51	-	-	-
BIS total score	66.45	10.07	59.33	6.51	0.01

Notes: Significant differences were found in BIS total scores between HD group and CN group. Abbreviation: HD: heroin dependent; CN: cognitive normal. SD: standard deviation. *p* values were obtained by an independent sample two-tailed *t* test. Unless otherwise indicated, data are presented as mean $\pm$ SD.

Table 2

Behavioral significance of intrinsic amygdala functional connectivity (iAFC) network

Side	Brain region	BA	Cluster Size (mm ³)	Talairach coordinates (LPI)			z score
				x	y	Z	
Heroin group							
Insula	R	13	1992	37	−17	16	4.61
PCC	R	29	1944	13	−47	15	3.37
Subcallosal gyrus	R	25/11	1640	8	14	−17	4.02
Thalamus	R		1592	11	−22	4	3.48
Fusiform area	L	37	2320	−45	−51	−12	−4.40
Control group							
Pre-SMA	L	6	1480	−21	−15	50	5.20
OFC	R	11	1440	7	−69	46	−4.23
Precuneus	R	7	1376	19	49	−12	−5.63

Notes: Linear regression analysis between amygdala network strength and BIS total scores across heroin subjects and control subjects, respectively, significant level was set at $p < 0.01$ with cluster size $> 1180 \text{ mm}^3$. Abbreviation: BA, Brodmann's area; x,y,z, coordinates of peak locations (highest z-values) in the Talairach space; r, regression coefficient; R, right; L, left; PCC, posterior cingulate cortex; Pre-SMA, pre-somamotor area; OFC, orbital frontal cortex.