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Effect of cocaine dependence on brain connections: Clinical implications

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Abstract

Cocaine dependence (CD) is associated with several cognitive deficits. Accumulating evidence, based on human and animal studies, has led to models for interpreting the neural basis of cognitive functions as interactions between functionally related brain regions. In this review, we focus on the magnetic resonance imaging (MRI) studies using brain connectivity techniques as related to CD. The majority of these brain connectivity studies indicated that cocaine use is associated with altered brain connectivity between different structures, including cortical-striatal regions and default mode network. In cocaine users, some of the altered brain connectivity measures are associated with behavioral performance, history of drug use, and treatment outcome. The implications of these brain connectivity findings to the treatment of CD and the pros and cons of the major brain connectivity techniques are discussed. Finally potential future directions in cocaine use disorder research using brain connectivity techniques are briefly described.

Keywords

cocaine use disorder; magnetic resonance imaging; functional connectivity; effective connectivity; brain connectivity

Introduction

Cocaine use disorder (CD) (See Table 1 for all abbreviations used in this article) is associated with several cognitive deficits [1–2]. Accumulating evidence from human and animal studies has led to models for interpreting the neural basis of cognitive functions as

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interactions between functionally related brain regions [3–6]. One of the theories is that CD affects three separate and interacting systems: the prefrontal cortex (PFC) dependent (reflective) system, the amygdala-striatum dependent (automatic, habitual or salient) system, and the insula system that translates interoceptive signals into conscious feelings of desire and decision-making processes related to uncertain risk and reward [7–8]. Imbalance among these systems has been theorized to contribute to compulsive substance use and loss of control in substance use disorders [7,9]. In addition, successful abstinence from drugs is associated with improvement in prefrontal structure and function [10], with likely improvement in the control of PFC over the striatal regions [10–11]. Furthermore, Robbins et al. [12] proposed 'neurocognitive endophenotypes', whereby changes in behavioral or cognitive processes are associated with deficits in neural systems. According to Robbins et al. [12], four 'frontostriatal loops' putatively associated with different aspects of impulsivity and compulsivity. Among these loops, two loops are relevant to impulsivity: i.e., the ventromedial PFC, subgenual cingulate cortex, ventral striatal loop associated with reward, and the ventrolateral PFC, ACC, pre-supplementary motor area, caudate, and putamen loop associated with stop-signal inhibition. Thus, brain connectivity analysis may be a potentially powerful tool to understand the neural correlates underlying impaired cognitive functions, and to test theories such as the aforementioned triple-system theory.

Magnetic resonance imaging (MRI) based brain connectivity analysis is generally classified into functional connectivity [13], effective connectivity [13], and structural connectivity [14]. Functional connectivity refers to the correlations between spatially remote neurophysiological events [13]. Unlike functional connectivity, effective connectivity models the causal effect that one region's activity has on another region [13]. Thus the direction of connectivity is determined in effective connectivity. Structural connectivity can be measured using white matter tractography, which is used to visually represent fiber tracts using MRI diffusion tensor imaging [14]. Figure 1 shows a schematic diagram illustrating structural connectivity (fiber pathways, top), functional connectivity (correlations, middle), and effective connectivity (causal relationship, bottom) among between two brain regions (R1 and R2).

In this article, we review MRI-based brain connectivity studies that investigated the effects of cocaine use in humans and animals with a focus on the aforementioned triple-system theory. We summarize the relationship between the altered brain connectivity measures and the behavioral performance, drug use history, and treatment outcomes in the CD subjects. We discuss the implications of the brain connectivity findings on the treatment of CD and the pros and cons of the major brain connectivity techniques used in these studies. Finally we discuss potentially useful future directions in CD research using brain connectivity.

Included studies and major findings

We searched http://www.ncbi.nlm.nih.gov/pubmed/ using the key words "cocaine connectivity MRI" and found 47 articles. The search date was June 1st 2015. Out of these, 33 articles used MRI-based brain connectivity analysis in chronic cocaine use. Therefore these 33 articles were included in this review. Thirty of these included studies on human subjects except for three in which monkeys or rats were used as the subjects. Twenty of

these 33 studies investigated resting state functional connectivity (rsFC) in humans. The study subjects, rsFC analysis methods, and the major findings of these rsFC human studies are summarized in Table 3. Ten of these 33 studies investigated functional connectivity or effective connectivity in humans during tasks. The study subjects, the task used, the brain connectivity analysis methods, and the major findings of these task-based brain connectivity studies are summarized in Table 4. Three of these 33 studies investigated rsFC in animals. The study subjects, rsFC analysis methods, and the major findings of these animal studies are summarized in Table 5. The detailed seed regions and/or regions of interest (ROIs) used are also provided for the brain connectivity analytical methods.

Resting state functional connectivity studies in humans

During resting state, cocaine-dependent subjects (CDs), cocaine abusers, or subjects with prenatal cocaine exposure (PCE), had greater or lower FC between different regions compared to non-drug-using controls (CTLs). These results are summarized in Table 3. As can be seen from Table 3, the results across the studies are not always consistent. The conflicting findings could be due to different methods [15], small sample size, different cohorts [14] used in different studies and/or multiple other unknown factors [14].

Task-based brain connectivity studies in humans

As summarized in Table 4, compared to CTLs, the CD subjects had greater or lower FC between different brain regions.

Three effective connectivity studies were conducted to investigate neural correlates underlying working memory [16], response inhibition [17], and cue reactivity [18] in CDs. Ma et al. [16] used dynamic causal modeling (DCM) of a working memory task and found that during short memory delay condition, the inferior frontal gyrus to striatum effective connectivity was reduced in CDs but increased in CTLs. During the longer memory delay condition, the middle frontal gyrus to striatum effective connectivity was more reduced in CDs than in CTLs [14]. In another functional magnetic resonance imaging (fMRI) based DCM study, Ma et al. [17] used a Go/NoGo task to test response inhibition in CDs and matched CTLs. Results of this study showed differences between groups in effective connectivity during the Hard NoGo condition: the effective connectivity from right (R) dorsolateral prefrontal cortex (DLPFC) to left (L) caudate was increased in CTLs but remained the same in the CDs; the effective connectivity from R ventrolateral prefrontal cortex to L caudate was reduced in the CTLs but remained the same in the CDs; the effective connectivity from L anterior cingulate cortex (ACC) to L caudate remained the same in the CTLs but was reduced in the CDs. Ray et al. [18] found that during cocaine-cue exposure of a cocaine-Stroop task, CDs had a particular feed-forward effective connectivity among the nodes of the drug-cue processing network (amygdala→hippocampus→dorsalstriatum→insula→medial frontal cortex, DLPFC, ACC) that was not present in the CTLs. All these effective connectivities had positive strength except for the connectivity from insula to medial frontal cortex. Consistent with the triple-system theory [7–8], these effective connectivity studies indicated that CD is associated with an imbalance among the PFC regions, insula, and striatal regions: weakened control of the

PFC regions over the striatal regions during working memory [16] and response inhibition [17] and strengthened control of the striatal and insular regions over the PFC regions during the cocaine-Stroop task [18].

Resting state functional connectivity studies in animals

Three resting state functional connectivity studies were conducted in rats [19–20] or monkeys [21]. The results are summarized in Table 5. Lu et al. [20] found that cocaine self-administration (SA) rats had lower rsFC between prelimbic cortex and entopeduncular nucleus and between nucleus accumbens core and dorsomedial PFC compared to both sucrose-SA and CTL rats. In addition, the rsFC between nucleus accumbens core and dorsomedial PFC was positively correlated with cocaine SA escalation in cocaine-SA rats. The other two studies investigated the acute effect of cocaine administration in cocaine-SA rats or cocaine-SA monkeys. Murnane et al. [21] found that acute cocaine administration selectively reduced the rsFC between ACC and nucleus accumbens, and between DLPFC and nucleus accumbens. In addition, the rsFC between DLPFC and nucleus accumbens during abstinence predicted cocaine intake when the monkeys were provided renewed access to cocaine [21]. Another animal study [19] also reported increased rsFC after acute cocaine administration. This was different from another study that reported decreased rsFC [21]. This difference may be related to the different species or seed regions used in the two studies.

Relationship between brain connectivity and behavior, drug use history, and treatment outcome

Greater impulsivity was found to be associated with higher rsFC between orbital frontal cortex and subgenual ACC [22], and between striatum and DLPFC [23]. Greater impulsivity was found to be associated with lower resting state inter-network connectivity between an intrinsic connectivity network involving the anterior insula and ACC, and an intrinsic connectivity network involving the striatum [24]. In addition, the rsFC between perigenual ACC and DLPFC was significantly and positively correlated with reversal learning score [25]. In [22], the authors first computed the rsFC between right ventral striatum (superior part) and anterior prefrontal cortex/orbitofrontal cortex (Go circuit) and the rsFC between right ventral striatum (inferior part) and dorsal anterior cingulate cortex (STOP circuit). The GO circuit is hypothesized to promote compulsive behaviors while the STOP circuit may limit such behaviors [22]. They then computed rsFC (difference) = rsFC (GO circuit) - sFC (STOP circuit) and performed a correlation analysis and found that rsFC (difference) was positively correlated with compulsive like behaviors reflected in the DSM-IV-TR in cocaine users. The greater difference in rsFC between striatal-anterior prefrontal/orbital frontal cortex (GO) and striatal-dorsal ACC (STOP) circuits was associated with more loss of control over cocaine use [23]. These studies suggest that the impaired cortical-striatal connectivity may be an underlying factor in the impaired behavioral performance in CD.

The duration of cocaine use was associated with lower rsFC between ventral tegmental area and thalamus/lentiform nucleus/nucleus accumbens [26], greater short-range and long-range functional connectivity density in the regions of the default mode network (DMN) [27],

lower intra-network connectivity strength of sensory motor cortex [28], and greater inter-network connectivity strength between occipital-limbic brain regions [28]. Greater peak cocaine level was associated with greater rsFC between caudate and thalamus and between amygdala and insula, and with lower rsFC between amygdala and cerebellum [22]. Greater recent cocaine use was associated with greater rsFC between striatum and DLPFC [23]. Greater cocaine use frequency and money spent on cocaine per week in abstinent CDs was associated with lower connectivity strength within occipital brain regions [28].

One study [29] compared rsFC across relapsed CDs, non-relapse CDs, and CTLs. The results of that study showed that relapsed CDs had lower rsFC between the L corticomedial amygdala and ventromedial PFC/rostral ACC than non-relapse CDs [29]. Adinoff et al. [30] found that rsFC between posterior hippocampus and posterior cingulate cortex (part of DMN) predicted relapse with 75% accuracy at 30, 60, and 90 days following treatment. During cocaine-Stroop tasks, greater Stroop-related intrinsic connectivity in bilateral thalamus, ventral striatum, and substantia nigra regions was associated with smaller number of self-reported days of consecutive abstinence during treatment [31]. In addition, greater Stroop-related intrinsic connectivity in bilateral thalamus, ventral striatum, and substantia nigra, R insula and L hippocampus was associated with more positive urine screens [31]. Greater effective connectivity from insula to DLPFC was associated with greater cocaine craving ratings [18]. In monkeys, impaired connectivity between PFC and striatal regions during abstinence predicted cocaine intake when the monkeys were able to access cocaine again [21]. These studies suggest that impaired cortical-striatal connectivity and DMN may be predictive of treatment outcomes.

Implication for the treatment of cocaine use disorder

The findings of the brain connectivity studies suggest that the cortico-striatal circuits could be therapeutic targets in CD. For example, Konova et al. [32] found that short-term methylphenidate (MPH) administration reduced an abnormally strong rsFC between ventral striatum and the dorsal striatum (putamen/globus pallidus), and lower rsFC between these regions with placebo administration robustly correlated with less severe addiction. In addition, short-term MPH strengthened several corticolimbic and corticocortical connections. Konova et al. [27] found that while the effects of MPH on functional connectivity density only partly overlapped with those of CD, MPH was associated with reduced density of short-range connections to the putamen/thalamus, a network of core relevance to habit formation and addiction [33]. These studies [27,32] did not report if the rsFC affected by the MPH is correlated with the clinical measures such as cocaine use or impulsivity. In addition to medications, deep brain stimulation (DBS) and repeated trans-cranial magnetic stimulation (rTMS) are two promising approaches which can be used for treating CD, with cortical-striatal circuits as the targets [11].

Expert Commentary

While activation measures or structural measures provide local information, the connectivity measures provide information about the relationship among distinct brain regions. Previous studies (reviewed by Rowe [34]) showed that the functional or effective connectivity

methods could be sensitive to the presence or severity of disease and/or treatment, even where activation analysis is insensitive. However, as suggested by Rowe [34], the connectivity methods should be used as complementary to, not a substitute for, the activation or structural measures.

The majority of the existing brain connectivity studies indicate that CD is associated with altered brain networks including cortical-striatal regions and DMN. Within the CD subjects, some of the altered brain connectivity measures are associated with behavioral performance, drug use history, or treatment outcomes. Some studies, e.g., Ma et al. [16,35], have speculated that the change of connection could be due to the effect of change of neurotransmitters. The direct “toxic” effect of cocaine could be another causal factor. Future studies are needed to test these hypotheses. Given the alterations reviewed here, it is an interesting topic to describe which of these alterations in connectivity are specific of CD, and which others are shared by consumption of other drugs of abuse.

The cortical-striatal circuits could be promising therapeutic targets for CD. There is a pressing need to develop clinically useful biomarkers for treatment or prognosis of substance use disorders [36–37]. To date, however, it is still one of the major challenges to identify such useful biomarkers [38]. Rowe [34] has demonstrated that the connectivity approaches are relatively more sensitive to the presence or severity of disease and/or treatment than the approaches of regionally specific dysfunction. Thus, brain connectivity approaches could be clinically useful biomarkers for the treatment or prognosis of cocaine use disorder although there is still a paucity of such studies in the literature of cocaine use disorder.

Resting state functional connectivity and task-based effective connectivity are the two major brain connectivity techniques used in the studies described above. During the resting state fMRI scan, the subject is not required to perform any task. Thus resting state design is particularly attractive for animal studies or studies on patients incapable of task performance during the scan. This is an advantage of the resting state design over the task-based design. However, some neuronal processes essential in CD studies can only be measured with task-based fMRI [39]. In addition, resting state fMRI data has relatively low signal to noise ratio and requires extensive preprocessing steps to increase the signal to noise ratio. One should choose either task-based or resting state or both designs depending on the research question. Functional connectivity, which is based on correlation, cannot provide the direction of connectivity. However, functional connectivity is generally easy to compute although more complicated methods such as the graph theoretical analysis have been prposed [40]. Functional connectivity analysis could be hypothesis driven [41] or data driven (e.g., ICA) [42]. Although originally, functional connectivity needed ROIs to compute the correlation coefficients, whole brain functional connectivity methods such as the modular analysis [43] are now available and eliminates this requirement. Effective connectivity can provide the direction of connectivity, which may be important for understanding the neurobiology of CD. Effective connectivity analysis is generally complicated. In its original implementation, effective connectivity was hypothesis driven, but currently data driven effective connectivity techniques such as the DCM network discovery [44–45] are available. Effective connectivity needs ROIs and whole brain effective connectivity technique available are not

yet available. DCM, one of the implementation of effective connectivity analysis, works on underlying neuronal level rather than at the hemodynamic level [46]. Therefore, confounders such as disease or medications may have less effect on the DCM analysis [46–49]. Originally, DCM was based on task-based fMRI data. However, currently novel DCM techniques have been developed for the analysis of resting state fMRI [50–52].

Five Year View

Almost all human studies reviewed here are cross sectional in nature. Thus, these studies cannot distinguish the preexisting altered brain connectivity from that caused by chronic cocaine use. Given the fact that both could be underlying factors, it is necessary to distinguish these two causes. Animal studies are particularly appropriate to address this question because the drug use can be well-controlled. Currently there are few brain connectivity studies in experimental CD. Resting state functional connectivity and structural connectivity analyses are particularly suitable for animal studies. Alternatively, longitudinal studies using non-treatment-seeking CD subjects can hopefully also address this question. However, we are not aware of any such publications.

Similarly, there exists the possibility that a remote region that has not been directly damaged shows a change of functional (or effective) connectivity. Such a phenomenon is called “connectional diaschisis” [53–54]. As suggested by Carrera and Tononi [54], the connectivity showing connectional diaschisis could be the target of therapeutic strategies. Brain lesion has been used to locate directly damaged brain region in [53]. For cocaine use disorder, brain regions showing altered structure or function could be used as directly damaged brain regions.

Functional connectivity and effective connectivity are related to white matter structural connectivity [55–56]. Previous MRI diffusion studies have reproducibly shown that CD is associated with significant white matter changes in both humans [57–63] and animals [64–65]. The impaired white matter integrity could be associated with impulsivity [57], poor decision-making [62], or worse treatment outcomes [66]. However, only one study [67] has used MRI diffusion-derived tractography to investigate the impaired structural connectivity in the PCE subjects.

Combined neuroimaging modalities can provide more information than a single imaging modality alone. Adinoff et al. [30] combined pseudo-continuous arterial spin labeling (pCASL) and resting state fMRI. These authors first analyzed the pCASL data to locate the region showing group difference in regional cerebral blood flow (rCBF). They then used this region as a seed for the resting state fMRI functional connectivity analysis. Coullaut-Valera et al. [68] used electroencephalography (EEG) to investigate impaired functional connectivity in polydrug users. EEG has low spatial resolution and high temporal resolution and so it is natural to combine it with fMRI which has a high spatial resolution, but relatively low temporal resolution, to gain more understanding of brain connectivity. A review [69] of 12 papers correlating EEG and fMRI-based resting state networks in adult human subjects suggests that spatially delimited theta and whole/local alpha waves could add important additional information to fMRI-based resting state networks (RSNs).

Combined fMRI-based functional/effective connectivity and MRI diffusion-based structural connectivity may provide additional insight for the relationship between brain structure and function [55,70]. Prior information provided by MRI diffusion-based tractography (structural connectivity) can improve the results of DCM effective connectivity analysis [71].

DCM could be used to understand the consequences of pathophysiological changes. For example, DCM has been used to explain how acetylcholine enhances the precision of bottom-up synaptic transmission in cortical hierarchies [72]. In another study, Moran et al. [73] used DCM to infer the synaptic basis of ketamine-induced change in coordinated oscillations in the neural circuits of the rat happocampus and PFC. The information provided in these studies suggests that it is possible to use DCM to quantify the putative synaptic mechanisms underlying certain drug effects in terms of changes in effective (directional) connectivity between brain regions.

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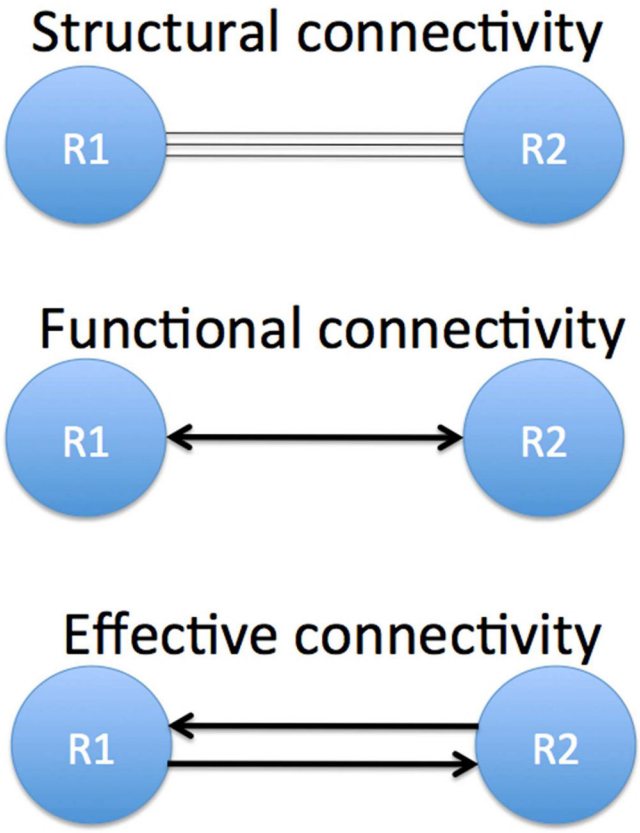

Figure 1.
Schematic diagram illustrating structural connectivity (fiber pathways, top), functional connectivity (correlations, middle), and effective connectivity (causal relationship, bottom) between two brain regions (R1 and R2).

Table 1

Abbreviations used in this manuscript.

Abbreviations	Definition
AB	attentional bias
AcbC	nucleus accumbens core
AcbS	nucleus accumbens shell
ACC	anterior cingulate cortex
BLA	basolateral amygdala
CCA	cross correlation analysis
CD	cocaine dependence
CDs	Cocaine dependent subjects
CMA	corticomedial amygdala
coc	cocaine
CPu	caudate putamen
CTLs	controls
DBS	deep brain stimulation
DC	dorsal caudate
DCM	dynamic causal modeling
DCP	dorsal caudal putamen
DLPFC	dorsolateral prefrontal cortex
DMN	default mode network
DMT	delayed memory task
DRP	dorsal rostral putamen
ECN	executive control network
EEG	electroencephalography
FC	functional connectivity
FCD	functional connectivity density
fMRI	functional magnetic resonance imaging
ICA	independent component analysis
ICD	intrinsic connectivity distribution
ICN	intrinsic connectivity networks
IFC	inferior frontal cortex
IFG	inferior frontal gyrus
IFS	inferior frontal sulcus
IMaGES	Independent Multi-sample Greedy Equivalence Search
IMT	immediate memory task
L	left
LR	bilateral
M1	primary motor cortex
MCC	middle cingulate cortex

Abbreviations	Definition
MDN	mediodorsal nucleus
MFC	medial frontal cortex
MFG	middle frontal gyrus
MPH	methylphenidate
MRI	magnetic resonance imaging
MTG	middle temporal gyrus
MTL	medial temporal lobe
NAC	nucleus accumbens
NCOC	utero exposure to non-cocaine drugs
OFC	orbital frontal cortex
PAG	periaqueductal gray
pCASL	pseudo-continuous arterial spin labeling
PCC	posterior cingulate cortex
PCE	prenatal cocaine exposure
PDE	prenatal drug exposure
PFC	prefrontal cortex
PGs	individuals with pathological gambling
pHp	posterior hippocampus
PPC	posterior parietal cortex
PPI	psychophysiological interaction
PrL	prelimbic cortex
R	right
ROIs	regions of interest
rsFC	resting state functional connectivity
RSN	resting state network
rTMS	repeated trans-cranial magnetic stimulation
S1	primary sensory cortex
S2	secondary sensory cortex
SA	self-administration
SFG	superior frontal gyrus
SMA	supplementary motor area
SN	salience network
STR	striatum
VLPFC	ventrolateral prefrontal cortex
VRP	ventral rostral putamen
VSi	inferior ventral striatum
VSs	superior ventral striatum
VTA	ventral tegmental area

Table 2

Connectivity techniques used in the studies reviewed in this manuscript.

Techniques	Brief introduction
Cross correlation analysis (CCA)	CCA is a method in which functional connectivity is measured by evaluating the correlation between the time course of each voxel (or region of interest) and a reference function (often obtained from a seed).
Dynamic causal modeling (DCM)	DCM is a Bayesian procedure that measures effective connectivity through optimally predicting how fMRI data were generated. The effective connectivity, which is formulated in terms of stochastic or ordinary differential equations, is modeled at the hidden neuronal level rather than the observed fMRI level.
Functional connectivity density (FCD)	It estimates the number of global and local functional connections to a given region that exceed a specified correlation strength, based on correlations among all voxels, and the number of remote (long-range) connections, which is the difference between the former two numbers.
Global connectivity analysis	It is a data-driven FC method. It is a quantitative measure of the extent each voxel is connected to every other voxel in the brain, based on a correlation coefficient matrix obtained from the correlation analysis among all voxels.
Graph theory	A graph consists of a set of nodes (or vertices) and a set of connections (or edges). The adjacency matrix A contains the information about the connectivity structure of the graph. $A_{i,j} = 1$ when an edge exists between two vertices i and j, otherwise $A_{i,j} = 0$. The number of edges connecting to a vertex is called the degree k of this vertex. In graph theory, efficiency provides a physical meaning for topological characterization of the networks and measures the ability of information transfer of a network. Efficiency can be measured at the local or global level. Small-worldness refers to a phenomenon that most nodes are not neighbors of one another. However, every other node can reach these nodes through a small number of steps (or hops).
Intrinsic connectivity density (ICD)	ICD is based on the correlation among all voxels of interest. For each voxel, a histogram of correlations is constructed to estimate the distribution of connections to this voxel. The alpha parameter, which controls the spread of the distribution of connections, is a measure of number of high-correlation connections. Group level analysis is conducted based on the parametric image of the alpha parameter from all voxels for each subject.
In dependent component analysis (ICA)	ICA is data-driven method for functional connectivity analysis, which drives a set of measurement data into a number of independent components (or maps). It requires no reference function or predefined seed.
Independent Multisample Greedy Equivalence Search (IMaGES)	IMaGES measures effective connectivity. Given a set of ROIs and without a prescribed model, IMaGES uses a Bayesian algorithm to search for the best model.
Modular analysis	Based on the correlations among all voxels, the modular analysis aims to find an optimal partition of modules, which are groups of nodes that are strongly connected with each other in the same module. After the modules are determined, both inter-module connectivity and intra-module connectivity are then computed.
Psychophysiological interaction (PPI)	PPI measures functional connectivity between a brain region and the rest of the brain with relation to the performance of a particular psychological task.

Table 3

Resting state functional connectivity in humans. See Table 1 for the abbreviations used in this table.

Study	Subjects	rsFC methods	Major findings
Adinoff et al. [30]	22 relapsed CDs, 18 early-remission CDs and 20 CTLs	Cross correlation analysis (CCA) with L pHp as the seed	• The relapsed CDs had greater rsFC between pHp and PCC/precuneus than early remission CDs. • The rsFC between pHp and PCC predicted relapse with 75% accuracy at 30, 60, and 90 days following treatment.
Camchong et al. [25]	27 CDs and 24 CTLs	CCA with subgenua, caudal, dorsal, rostral, perigenual ACC as seeds	• CDs had greater rsFC between perigenual ACC and DLPFC, MTG, and SFG than CTLs. • In CDs, FC between perigenual ACC and DLPFC as significantly positively correlated with reversal learning score.
Cisler et al. [74]	41 CDs and 19 CTLs	In dependent component analysis (ICA) & CCA with R ventral anterior insula, R mid-insula as seeds	• CDs had greater rsFC between R ventral anterior insula and R IFG and dorsomedial PFC. • CDs had greater rsFC between R mid-insula and LR DLPFC and lower between R mid-insula and dorsal posterior insula.
Contreras-Rodriguez et al. [22]	20 CDs, 19 PGs, and 21 CTLs	Global connectivity analysis & CCA with OFC, L and R caudate, amygdala, thalamus as the seeds	• CDs had greater global connectivity in OFC, caudate, thalamus and amygdala than PGs. • CDs had greater rsFC between the OFC and subgenual ACC and between caudate and lateral PFC than PGs. • CDs and PGs had greater rsFC between the OFC and the dorsomedial PFC and striatum, and between the amygdala and insula than CTLs. • In CDs, rsFC between OFC and subgenual ACC was correlated with impulsivity and greater severity of peak cocaine was associated with greater rsFC between caudate and thalamus, between amygdala and insula, and lower rsFC between amygdala and cerebellum.
Gu et al. [26]	39 cocaine users (34 current CDs, 4 current cocaine abusers, 1 current recreational user) and 39 CTLs	CCA with NAC, amygdala, hippocampus, medial dorsal thalamus, and rostral ACC as seeds	• CDs had lower rsFC between VTA and a region encompassing thalamus/lentiform nucleus/NAC, between amygdala and medial PFC, and between hippocampus and dorsal medial PFC. • In CDs, the strength of the functional connectivity between VTA and thalamus/lentiform nucleus/NAC was negatively correlated with years of cocaine use.
Hu et al. [23]	56 cocaine users (53 CDs and 3 cocaine abusers) and 56 CTLs	CCA with VSi, VSs, DC, VRP, DRP, DCP as seeds	• Cocaine users had lower rsFC between VSi seed dorsal part of ACC and the superior temporal gyrus. • Lower rsFC between the VSs seed and dorsal ACC and ventral striatum. • Greater rsFC between DC seed and LR DLPFC. • Lower rsFC between VRP and a large portion of L putamen, and between VRP and occipital cortex. • Lower rsFC between DRP and dorsal ACC, and between DRP and LR insula. • Lower rsFC between DCP and MCC, and between DCP and L putamen. • In the cocaine users, greater striatal-dorsal lateral PFC connectivity strength was positively correlated with the greater amount of recent cocaine use and elevated trait impulsivity.

Study	Subjects	rsFC methods	Major findings
			• The difference of rsFC between striatal-anterior prefrontal/OFC (GO) and striatal-dorsal ACC (STOP) circuits was significantly positively associated with loss of control over cocaine use
Kelly et al. [75]	25 CDs and 24 CTLs	CCA with L and R IFS as seeds	• CDs had lower rsFC between R IFS seed and L lateral PFC and premotor cortex. • Lower rsFC between L IFS and R PPC and intra parietal sulcus. • In CDs, rsFC within the dorsal attention network was associated with self-reported attentional lapses.
Konova et al. [32]	18 cocaine users (17 CDs and 1 cocaine abusers) and 16 CTLs	CCA with L and R VTA, NAC, amygdala, hippocampus, MDN of thalamus, rostral ACC as seeds	• CDs had greater rsFC between R NAC and L putamen/globus pallidus. • Short-term MPH administration reduced above abnormally strong rsFC. • Lower rsFC between R NAC and L putamen/globus pallidus during placebo administration was associated with less severe addiction. • Short-term MPH strengthened several corticolimbic and corticocortical rsFC.
Konova et al. [27]	19 cocaine users (18 CDs and 1 cocaine abuser) and 15 CTLs	Functional connectivity density (FCD)	• Cocaine users had greater short-range and long-range FCD in the ventromedial PFC, posterior cingulate/precuneus, and putamen/amygdala, which in areas of DMN correlated with years of use. • MPH decreased short-range FCD in the thalamus/putamen, and long-range FCD in SMA and postcentral gyrus.
Li et al. [76]	33 PCE adolescents and 23 CTL adolescents	ICA & CCA with PCC as seed	• PCE group had greater rsFC in DMN, including medial PFC, parahippocampal gyrus, anterior and posterior cingulate regions, and lateral parietal areas, than CTLs.
Liang et al. [43]	47 CDs and 47 CTLs	Modular analysis	• CDs had lower inter-module connectivity between DMN and SN. • CDs had lower average connectivity between the rostral ACC and SN, between rostral ACC and MTL, between the posterior cingulate and ECN, and between LR insula and DMN. • In CDs, intra-module connectivity within SN was negatively correlated with alexithymia, a personality trait previously associated with addiction.
McHugh et al. [77]	45 CDs and 22 CTLs	CCA with L and R caudate, putamen, NAC as seeds	• CDs had lower rsFC between LR putamen and posterior insula and R postcentral gyrus than CTLs. • CDs had higher impulsivity (BIS-11a) scores than CTLs, which was partially mediated by the lower putamen-posterior insula rsFC in CDs.
McHugh et al. [29]	24 relapsed CDs, 21 non-relapse CDs, and 22 CTLs	CCA with L and R BLA, CMA as seeds	• Relapsed CDs had lower rsFC between the L CMA and ventromedial PFC/rostral ACC than non-relapse CDs. • Non-relapse CDs had lower rsFC between LR BLA and visual processing regions (lingual gyrus/ cuneus) than CTLs and relapsed CDs.
Ray et al. [28]	20 CDs and 17 CTLs	ICA & CCA with 61 ROIs	• CDs had greater rsFC within sensory motor cortex and L frontal-parietal network than CTLs. • CDs had greater inter-network rsFC between frontal-temporal and frontal-parietal brain regions, and lower rsFC between parietal-parietal, occipital-limbic, occipital-occipital, and occipital-parietal brain regions.

Study	Subjects	rsFC methods	Major findings
			• In CDs, intra-network connectivity strength of sensory motor cortex was negatively correlated with years of cocaine use; inter-network connectivity strength between occipital-limbic brain regions was positively correlated with years of cocaine use, and connectivity strength within occipital brain regions was negatively related to cocaine use frequency and money spent on cocaine per week in abstinent CDs.
Salzwedel et al. [78]	33 PCE infants, 40 NCOC infants and 46 CTLs	CCA with insula, amygdala, L and R visual cortices as seeds	• Common drug exposure-related rsFC disruptions were within the amygdala–frontal, insula–frontal, and insula–sensorimotor circuits. • PCE infants had greater rsFC in a subregion of the amygdala–frontal network than infants with NCOC and CTLs.
Schweitzer et al. [79]	27 PDE adolescents (with intrauterine exposure to cocaine and/or heroin) and 20 CTLs	Graph theory	• The PDE group had lower global efficiency than the CTLs and a trend level reduction in local efficiency. • The network node corresponding to MFG group by task interaction showed reduced nodal efficiency and fewer direct connections to other nodes in the network.
Verdejo-Garcia et al. [80]	10 CDs and 14 CTLs	CCA with ACC, PAG, insula as seeds	• CDs had lower rsFC between ACC, thalamus, insula and brain stem than CTLs.
Wang et al. [40]	20 poly drug users (the primary diagnosis was cocaine dependence) and 19 CTLs	Graph theory using 90 ROIs	• Among the assessed 90 ROIs, the drug users had stronger functional connectivity than the CTLs. • After controlling functional connectivity difference and the resultant network density, the drug users showed lower communication efficiency and reduced small-worldness than CTLs.
Wisner et al. [24]	33 CDs and 32 CTLs	ICA	• The inter-network connectivity between an ICN involving the anterior insula and ACC, and an ICN involving the striatum, was significantly weaker in CDs relative to CTLs. • In CDs, lower inter-network connectivity was significantly related to greater non-planning impulsivity.

Table 4

Task-based brain connectivity studies in humans. See Table 1 for the abbreviations used in this table.

Study	Subjects	Task, and brain connectivity methods	Major findings
Albein-Urios et al.	18 CDs with comorbid Cluster B personality disorders, 17 CDs without comorbidities and 21 CTLs	Re-appraisal task, Psychophysiological interaction (PPI) with subgenual ACC, OFC as ROIs	• During maintenance, comorbid CDs had lower FC between subgenual ACC and amygdala and fusiform gyri, greater FC between subgenual ACC and anterior insula than non-comorbid CDs. • During reappraisal, comorbid CDs had greater FC between L OFC and amygdala, and lower FC between R OFC and dorsal striatum.
Albein-Urios et al. [82]	17 CDs and 18 CTLs	Re-appraisal task, PPI with R DLPFC, R IFG as ROIs	• CDs had greater FC between DLPFC and LR posterior sensory regions, LR fusiform gyrus, LR medial frontal gyrus, R amygdala, inferior temporal and OFC,R insula/putamen regions during Maintain>Observe. • CDs had lower FC between R IFG and amygdala during Suppress>Maintain.
Hanlon et al. [83]	14 CDs and 15 CTLs	Finger-sequencing task, CCA with L M1, SMA, ACC, caudate, putamen, thalamus, R cerebellum as ROIs	• DCs had lower FC between SMA and caudate, and between SMA and putamen than CTLs. • In CDs, lower FC between SMA and caudate was associated with higher reaction time.
Kilts et al. [84]	42 CDs	Cocaine-Stroop task, ICA	• Variation in the attentional bias effect was related to the recruitment of two separate neural processing networks: inferior frontal–parietal–ventral insula network (related to stimulus attention and salience attribution), and frontal–temporal–cingulate network (related to the processing of the negative affective properties of cocaine stimuli). • Recruitment of a sensory–motor–dorsal insula network was negatively correlated with the drug attentional bias effect associated with cocaine dependence (AB-coc). • The activation of the frontal–temporal–cingulate network was correlated with the attentional bias effect for cocaine stimuli and for negative affective word stimuli.
Ma et al. [16]	19 CDs and 14 CTLs	IMT/DMT verbal working memory task, DCM with L IFC, L MFG, L PPC, R PPC, LR SMA, L STR, R STR as notes	• During IMT (short memory delay) condition, the IFC to L striatum effective connectivity was reduced in CDs but increased in CTLs. • During DMT (long memory delay) condition, the MFG to striatum effective connectivity was more reduced in CDs than in CTLs.
Ma et al. [17]	13 CDs and 10 CTLs	Go/NoGo response inhibition task, dynamic causal modeling DCM with L DLPFC, R DLPFC, L ACC, R ACC, R VLPFC, L caudate, R hippocampus as nodes	• During the Easy NoGo condition, the change of the effective connectivity from L ACC to L caudate was similar for both groups. • During the Hard NoGo condition, the effective connectivity from R DLPFC to L caudate increased in CTLs but remained the same in the CDs; the effective connectivity from R VLPFC to L caudate reduced in the CTLs but remained the same in the CDs; the effective connectivity from L ACC to L caudate remained the same in the CTLs but reduced in the CDs.
Mitchell et al. [31]	15 CDs and 15 CTLs	Cocaine-Stroop task, Intrinsic connectivity density (ICD)	• CDs had lower Stroop-related ICD in cortical and subcortical regions than CTLs.

Study	Subjects	Task, and brain connectivity methods	Major findings
			• When adjusting for individual degree of intrinsic connectivity, CDs had relatively greater ICD in the ventral striatum, putamen, IFG, anterior insula, thalamus and substantia nigra than CTLs. • In CDs, non-mean-adjusted ICD in bilateral thalamus, ventral striatum, and substantia nigra regions was negatively correlated with the maximum number of self-reported days of consecutive abstinence during treatment. • Non-mean-adjusted ICD in bilateral thalamus, ventral striatum, substantia nigra, right insula and left hippocampus was positively correlated with the percentage of positive urine screens.
Ray et al. [18]	20 CDs and 17 CTLs	Cocaine-Stroop task, Independent Multisample Greedy Equivalence Search (IMaGES) S with LR amygdala, R hippocampus, LR dorsal striatum, LR insula, LR MFC, LR OFC, L DLPFC, ACC, R ventral striatum as nodes	• During cocaine-cue exposure, CDs showed a particular feed-forward effective connectivity pattern among the nodes of the drug-cue processing network (amygdala→hippocampus→dorsalstriatum→insula→MFC, DLPFC, ACC) that was not present when the CTLs viewed the cocaine cues. • All above effective connectivities had positive strength except the effective connectivity from insula to MFC. • In CDs, cocaine craving ratings were positively correlated with the strength of the effective connectivity from the insula to DLPFC.
Tomasi et al. [85]	20 CDs and 20 CTLs	Cocaine-Stroop task, CCA with substantia nigra as seed	• CDs had lower (positive) FC between substantia nigra and thalamus, cerebellum, and rostral cingulate. • This lower FC was associated with decreased activation in thalamus and cerebellum and enhanced deactivation in rostral cingulate.
Worhunsky [86]	20 CDs and 20 CTLs	Cocaine-Stroop task, ICA	• CDs displayed less engagement of a “top-down” fronto-cingulate network (contributing to conflict monitoring), and more engagement of two “bottom-up” subcortical and ventral prefrontal networks (related to cue-elicited motivational processing) than CTLs. • In CDs, less engagement of the fronto-cingulate network was associated with better treatment retention; greater engagement of subcortical and ventral prefrontal networks was associated with abstinence during treatment.

Table 5

Resting state functional connectivity in animals. See Table 1 for the abbreviations used in this table.

Study	Subjects	rsFC methods	Major findings
Chen et al. [19]	7 cocaine SA rats, 5 saline SA rats, and 5 drug naïve rats.	CCA with CPu, M1, S1, S2, medial PFC, thalamus, insula as seeds	• After acute cocaine challenge, the cocaine SA rats had greater rsFC in the S1, medial PFC, and thalamus than the saline SA rats.
Lu et al. [20]	13 cocaine SA rats, 13 sucrose SA rats, and 22 sedentary CTL rats	CCA with PrL, ACC, AcbC, AcbS, CPu as seeds	• Cocaine-SA rats had lower rsFC between PrL and entopeduncular nucleus and between AcbC and dorsomedial PFC than both sucrose-SA and CTL rats. • The FC between Acb and dorsomedial PFC was positively correlated to cocaine SA escalation in cocaine-SA rats.
Murnane et al. [21]	3 cocaine SA adult monkeys	CCA with NAC, amygdala, DLPFC, ACC, cerebellum as seeds	• Acute cocaine administration selectively reduced the rsFC between ACC and NAC, and between DLPFC and NAC. • Impaired connectivity between DLPFC and NAC during abstinence predicted cocaine intake when the monkeys were provided renewed access to cocaine.