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A hyper-connected but less efficient small-world network in the substance-dependent brain

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ABSTRACT

Background: The functional interconnections of the addicted brain may differ from the non-addicted population in important ways, but prioranalytic approaches were usually limited to the study of connections between a few number of selected brain regions. Recent approaches enable examination of the vast functional interactions within the entire brain, the functional connectome (FCM). The purpose of this study was to characterize FCM alterations in addiction using resting state functional Magnetic Resonance Imaging (rsfMRI) and to assess their relations to addiction-related symptoms.
Methods: rsfMRI data were acquired from 20 chronic polydrug users whose primary diagnosis was cocaine dependence (DRUG) and 19 age-matched non-drug using healthy controls (CTL). FCM was assessed using graph theoretical analysis.
Results: Among the assessed 90 brain subdivisions, DRUG showed stronger functional connectivity. After controlling functional connectivity difference and the resultant network density, DRUG showed reduced communication efficiency and reduced small-worldness.
Conclusions: The increased connection strength in drug users' brain suggests an elevated dynamic resting state that may enable a rapid, semi-automatic, execution of behaviors directed toward drug-related goals.The reduced FCM communication efficiency and reduced small-worldness suggest a loss of normal inter-regional communications and topology features that makes it difficult to inhibit the drug seeking behavior.

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1. Introduction

Drug addiction is a chronic relapsing disorder that affects the brain structures and functions (Koob and Volkow, 2010). While functional neuroimaging investigations have contributed significant information about addiction-related brain differences in focal brain regions and systems (Hong et al., 2009; Janes et al., 2012; Lindsey et al., 2003; Ma et al., 2010; Volkow et al., 2003), less work has been done examining the complex brain network and connectivity patterns of multiple brain regions, though those properties may reflect the (acute or chronic) impact (Bullmore and Sporns, 2009; Rubinov and Sporns, 2010) of drug exposure. Assessing them may provide new insights about the addicted brain state, offering an expanded framework for examining the neuronal underpinnings of substance dependence.

Brain networks can be assessed using fMRI (Bullmore and Sporns, 2009; Rubinov and Sporns, 2010) and graph theoretical analysis (GTA; Watts and Strogatz, 1998). Reliable functional connectome (FCM) topological properties have been demonstrated in the healthy brain (Achard et al., 2006) with high test–retest stability (Braun et al., 2012; Wang et al., 2011). In drug addiction, FCM analysis has been applied in heroin and methamphetamine abusing populations, and these published reports showed inconsistent results with both larger or smaller FCM properties in drug addicted brain (Ahmadlou et al., 2013; Jiang et al., 2013; Liu et al., 2011a). Meanwhile, several seed-based FC studies have shown poor connectivity between frontal and limbic areas (Gu et al., 2010; Hong et al., 2009; Kelly et al., 2011; Ma et al., 2010). It is then not clear whether FCM analysis will echo with the prior seed-based

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Table 1
Demographic data for participants.

	Patients (n = 20)	Controls (n = 19)
Age (yrs)	42.15 ± 4.3	39.9 ± 4.5
Education (yrs)	12.07 ± 1.7	14.9 ± 2.9
Gender	20 males	19 males
Cocaine dependence severity	7.26 ± 1.76	0
Alcohol dependence severity	2.68 ± 2.54	0
Marijuana dependence or abuse	2	0
Drug craving score	0 ~ 3, 0.28 ± 0.83	0
Cigarette per day	7.67 ± 6.0	0
Smoking duration (yrs)	15.61 ± 12.1	0

connectivity analysis results, or whether new patterns will be evident when the brain's interconnections are considered as a whole. In the current study, we examined addiction-related FCM using resting-state fMRI (rsfMRI) in a drug abusing sample of patients with a primary diagnosis of cocaine dependence (DRUG) and compared to FCM in a demographically-similar control group (CTL) to identify potential addiction-related variations.

2. Materials and methods

2.1. Subjects

Twenty drug patients (age 42.15 ± 4.3 (mean ± standard deviation (std)), years of education 10.07 ± 1.7 all African–American men) with a DSM-IV diagnosis of cocaine dependence and 19 and age/ethnicity/race-matched controls (CTL) were recruited from the local community of West Philadelphia (age: 39.9 ± 4.5; education: 14.9 ± 2.9 yrs; all African–American men). The two groups were matched in age (p = 0.13 for the age difference). CTL had more years of education than DRUG (p = 0.0006). Detailed demographic data were listed in Table 1. The patients were treatment-seeking for cocaine-addiction, but defined by the M.I.N.I. (Sheehan et al., 1998), 6 patients had a diagnosis of alcohol dependence; 2 with alcohol abuse; 1 had marijuana dependence; and 2 had marijuana abuse.Therefore, for inferences in this initial connectome study, they are best-characterized as poly-substance abusers.

All subjects underwent full physical and psychological examinations. Severity of drug dependence was assessed using the addiction severity index (ASI; McLellan et al., 1980). Patients were not using medications that may cause sedation or are known to modify brain dopamine systems during the previous 60 days; had no cardiovascular, hematologic, hepatic, renal, neurological or endocrinological abnormalities; no history of head trauma or injury; no gambling problems; no history of psychosis or organic brain syndrome unrelated to drug abuse; and no other severe psychiatric disorders, with the exception of dependence on other substance as described above. Patients had 4–8 days of residential stabilization prior to study entry, during which they were drug-free, verified by urine drug screens. CTL were not dependent on any substances including alcohol and nicotine. Drug craving scores were recorded before the MRI scan using the Brief Substance Craving Scale (Somoza et al., 1995).

2.2. MRI data acquisition

MR imaging was conducted in a 3-T whole-body scanner (Siemens, Erlangen, Germany). High-resolution structural images were acquired for spatial brain normalization using a 3D MPRAGE sequence (TR/TE/TI = 1620/3/950 ms). rsfMRI images were acquired using a gradient-echo echo-planar-imaging sequence with parameters of: TR/TE = 2s/30 ms, FOV = 220 × 220 mm^2, matrix = 64 × 64 × 32, slice thickness = 4.5 mm. Participants were asked to lie still in the scanner at rest and keep their eyes open. 180 images were acquired.

2.3. Image preprocessing

All data preprocessing was performed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm) -based batch scripts (Wang et al., 2008) with the following steps: motion correction, coregistration, and normalization. Next, rsfMRI images were detrended to remove the linear and quadratic signal drift. Head motion time courses, the mean cerebral spinal fluid (CSF) and mean white matter signal were regressed out from each voxel's time series (Fair et al., 2008). The volume-to-volume displacement of each rsfMRI acquisition was calculated using the method proposed in (Power et al., 2012). The mean displacement of all acquisitions was taken as an indicator of the gross motion. A two-sample t-test was performed and showed no significant motion difference between patients and controls (p = 0.25). To further reduce motion effects, acquisitions with a volume-to-volume displacement >0.5 were excluded from further FCM analysis (Power et al., 2012). The number of excluded images did not show significant difference between the two groups (p = 0.4). rsfMRI images were also filtered using a passband of 0.01 Hz–0.08 Hz. No spatial smoothing was applied to prevent introducing artificial correlations. The rsfMRI images were then registered into the high-resolution structural images and subsequently into the MNI standard space using SPM8 (Ashburner, 2007).

2.4. Anatomical parcellation

rsfMRI time series were extracted from the preprocessed images from 90 regions (45 for each hemisphere, see Table 2 for the subdivision labels) as defined by the automated-anatomically-labeled (AAL) brain template (Tzourio-Mazoyer et al., 2002), which is widely used in FCM analysis(Achard et al., 2006). Since some of our resting state fMRI acquisition did not cover the entire cerebellum, we did not consider the cerebellum subdivisions in AAL during FCM analysis. The gravity center of each subdivision was used as its surrogate node.

2.5. Network construction

Pearson correlation coefficients (CC) of rsfMRI time courses were calculated for any pair of nodes. CC matrix was converted into a binary one using a threshold from 0.05 to 0.60 with a step of 0.01. The resulting binary matrix was used to build an undirected graph model G of the brain network (Watts and Strogatz, 1998). To visualize the FCM difference, a $p < 0.01$ (corrected for multiple comparisons using the false discovery rate (FDR) theory (Genovese et al., 2002) was used to find the corresponding CC threshold for all subjects and the maximum of them (across all subjects) (which was 0.26) was used as the final threshold to dichotomize the 90 × 90 CC matrix and build the FCM.

FCM topological properties rely on the network density, which is reliant on the connectivity strength. Populational connectivity difference may then affect topological FCM comparisons. To control network density difference, the CC matrix was also thresholded to have the same network density (sparsity) and was used for the subsequent FCM analysis. While sparsity thresholding would affect FCM properties especially when it is high, a between-group comparison should still be valid if the same threshold is used for both groups.

2.6. FCM measures

The following FCM measures (Rubinov and Sporns, 2010) were calculated using the brain connectivity toolbox (www.brain-connectivity-toolbox.net/):

2.6.1. Cost. The number of connections to a node was counted as its degree. The mean degree of all nodes reflects the density of a network.

2.6.2. Segregation measures. Segregation refers to splitting the brain into functionally specialized but densely interconnected sub-regions (a sub-group of nodes here). Each such sub-group is referred to as a clique. The clustering coefficient of a node is the fraction of its neighbors that are also neighbors of each other (Watts and Strogatz, 1998); the mean clustering coefficient C_p of all nodes reflects the prevalence of local clusters ("cliquishness") of the network: $0 \le C_p \le 1$, with $C_p = 1$ meaning each node is connected to all others. Local efficiency of a node is the average inverse shortest-path length (Latora and Marchiori, 2001) between the node pairs in the node's nearest neighborhood. Mean local efficiency (mLE) of all nodes is related to C_p.

2.6.3. Measures of network integration. Integration means unifying different sub-regions (a sub-group of nodes here) into a single functional entity and is usually characterized with paths that connect distinct nodes (Rubinov and Sporns, 2010) with shorter path representing stronger integration potential. The characteristic path length L_p is defined as the average shortest-path length between all pairs of nodes in the network (Watts and Strogatz, 1998). A related integration measures is the global efficiency (GE) E_{global} and is defined as the average inverse shortest-path length (Latora and Marchiori, 2001).

2.6.4. Small-worldness is computed by comparing the real network to random networks with the same number of nodes and average degree.

$$\sigma = \frac{C_p^{\text{real}}/C_p^{\text{rand}}}{L_p^{\text{real}}/L_p^{\text{rand}}}$$

Superscript "real" means from real data; "rand" means from random data.

(Humphries and Gurney, 2008; Watts and Strogatz, 1998). Random networks were generated using the random rewiring procedure proposedin(Maslov and Sneppen, 2002). Small-worldness measures the segregation and integration balance. A "small-world network" has $\sigma > 1$, which is more clustered (with higher C_p) than random networks, but has approximately the same L_p as that of a random network (Watts and Strogatz, 1998).

2.7. Patient versus (vs) control comparisons

DRUG-CTL FCM difference was examined using two sample-t testing at each threshold. Age was included as nuisance covariates.

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