Impaired Functional Connectivity Within and Between Frontostriatal Circuits and Its Association With Compulsive Drug Use and Trait Impulsivity in Cocaine Addiction

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IMPORTANT Converging evidence has long identified both impulsivity and compulsivity as key psychological constructs in drug addiction. Although dysregulated striatal-cortical network interactions have been identified in cocaine addiction, the association between these brain networks and addiction is poorly understood.

OBJECTIVES To test the hypothesis that cocaine addiction is associated with disturbances in striatal-cortical communication as captured by resting-state functional connectivity (rsFC), measured from coherent spontaneous fluctuations in the blood oxygenation level-dependent functional magnetic resonance imaging signal, and to explore the relationships between striatal rsFC, trait impulsivity, and uncontrolled drug use in cocaine addiction.

DESIGN, SETTING, AND PARTICIPANTS A case-control, cross-sectional study was conducted at the National Institute on Drug Abuse Intramural Research Program outpatient magnetic resonance imaging facility. Data used in the present study were collected between December 8, 2005, and September 30, 2011. Participants included 56 non–treatment-seeking cocaine users (CUs) (52 with cocaine dependence and 3 with cocaine abuse) and 56 healthy individuals serving as controls (HCs) matched on age, sex, years of education, race, estimated intelligence, and smoking status.

MAIN OUTCOMES AND MEASURES Voxelwise statistical parametric analysis testing the rsFC strength differences between CUs and HCs in brain regions functionally connected to 6 striatal subregions defined a priori.

RESULTS Increased rsFC strength was observed predominantly in striatal-frontal circuits; decreased rsFC was found between the striatum and cingulate, striatal, temporal, hippocampal/amygdalar, and insular regions in the CU group compared with the HCs. Increased striatal-dorsal lateral prefrontal cortex connectivity strength was positively correlated with the amount of recent cocaine use (uncorrected \( P < .046 \)) and elevated trait impulsivity in the CUs (uncorrected \( P < .012 \)), and an index reflecting the balance between striatal-dorsal anterior cingulate cortex and striatal-anterior prefrontal/orbitofrontal cortex circuits was significantly associated with loss of control over cocaine use (corrected \( P < .012 \)).

CONCLUSIONS AND RELEVANCE Cocaine addiction is associated with disturbed rsFC in several specific striatal-cortical circuits. Specifically, compulsive cocaine use, a defining characteristic of dependence, was associated with a balance of increased striatal-anterior prefrontal/orbitofrontal and decreased striatal-dorsal anterior cingulate connectivity; trait impulsivity, both a risk factor for and a consequence of cocaine use, was associated with increased dorsal striatal-dorsal lateral prefrontal cortex connectivity uniquely in CUs. These findings provide new insights toward the neurobiological mechanisms of addiction and suggest potential novel therapeutic targets for treatment.
Drug addiction is a chronic, relapsing brain disorder characterized by compulsive drug seeking and taking. As a feature commonly associated with drug addiction, impulsivity is a risk factor for and is worsened by cocaine use. In contrast, compulsive drug use is a cardinal feature of the disease. Both impulsivity and compulsivity are associated with abnormal fronto-striatal structures in cocaine users (CUs). In addition, extensive preclinical literature suggests a critical striatal role in cocaine addiction. Within striatum, a progressive change from mostly ventral to more dorsal processing domains occurs concurrent with the gradual development of compulsive drug consumption. For example, following chronic cocaine self-administration, the spatial extent and magnitude of neuronal activity as measured by glucose metabolism expands in an orderly fashion from the ventral striatum (VS) to encompass the dorsal striatum (DS). Cross-sectional human studies also implicate the striatum in cocaine addiction, as evidenced by striatal activation in response to cocaine administration. Striatal dopamine changes in response to cocaine self-administration, the spatial extent and magnitude of neuronal activity as measured by glucose metabolism expands in an orderly fashion from the ventral striatum (VS) to encompass the dorsal striatum (DS). Cross-sectional human studies also implicate the striatum in cocaine addiction, as evidenced by striatal activation in response to cocaine administration.

Anatomically, the striatum receives both glutamatergic and dopaminergic projections from multiple cortical and midbrain regions, respectively. The VS (generally including the nucleus accumbens, ventral parts of both caudate and putamen) receives major projections from orbitofrontal cortex (OFC), medial prefrontal cortex (mPFC), anterior PFC (aPFC), anterior cingulate cortex (ACC), and temporal and limbic structures. The dorsal striatal division has been divided into a dorsomedial portion (putamen), which receives projections primarily from sensory and motor areas. The VS also receives dopaminergic inputs primarily (but not exclusively) from the ventral tegmental area, and the DS receives dopaminergic afferents from the substantia nigra. The seminal work of Haber and Knutson has identified a spiral or looplike organizational relationship within striatal circuits such that the terminal field of diffuse projections from each cortical/midbrain area progressively extends throughout other regions of the striatum. Such a spiral organization suggests a striatal integration of afferent information from numerous brain regions thought to facilitate learning and response flexibility.

Compulsive drug seeking and taking are hallmarks of addiction, and 5 of 7 diagnostic criteria in the DSM-IV-TR concern loss of control over one's drug use. From a dual-process perspective, such compulsive behaviors can be thought to arise from an excessive drive (“go”) process for drug seeking and/or impaired control (“stop”) process to inhibit use. Relatedly, increased resting-state functional connectivity (rsFC) between VS and lateral aPFC/OFC has been observed to positively correlate with compulsive symptoms in obsessive-compulsive disorder (OCD). Increased rsFC between VS and OFC is also observed in cocaine addiction; however, its relationship to loss of control over drug use is unknown. Given the fact that compulsive drug use has phenotypic similarity with compulsions in patients with OCD, increased rsFC in VS-aPFC/OFC may reflect an excessive go process driving compulsive behaviors in these 2 disorders. In contrast, decreased rsFC between VS and the dorsal ACC (dACC) negatively correlates with nicotine dependence severity, which may reflect a weakened stop process since the dACC has long been suggested as a critical cognitive control region and shows hypoactivity and hyperactivity during inhibitory control tasks in active drug users and those with successful long-term abstinence, respectively. Despite substantial preclinical evidence of a ventral to dorsal shift in processing as drug use becomes compulsive or habitual, in humans the VS continues to activate to drug cues even after cocaine dependence has been well established. We therefore conjecture that this weakened VS-dACC circuit, originally identified in smokers, may also be present in individuals with cocaine dependence and relate to impaired control of urges to use drugs. Because both compulsive and impulsive processes likely play a role in cocaine addiction, it may well be the balance between go and stop circuits that captures the totality of the uncontrolled drug use phenotype better than either single circuit alone (ie, excessive go or impaired stop).

The goal of the present study was to investigate alterations in striatal circuits in CUs and how these alterations relate to key features of cocaine dependence. Building on previous reports, we tested the hypothesis that CUs have altered striatal rsFC compared with healthy individuals serving as controls (HCs). We then explore the relationship between striatal connectivity and self-reported trait impulsivity as measured by the Barratt Impulsiveness Scale, version 11 (BIS-11) and loss of control over cocaine use as measured by DSM-IV-TR substance dependence criteria items 3 to 7. In particular, based on phenotypic similarities with OCD and nicotine dependence, we further hypothesized increased rsFC in a VS-aPFC/OFC (go) circuit as well as reduced rsFC in a VS-dACC (addiction-related stop) circuit in CUs and that the balance between these circuits would predict loss of control over cocaine use.

Methods

Participants
A case-control, cross-sectional study was conducted at the National Institute on Drug Abuse Intramural Research Program outpatient magnetic resonance imaging facility; data used in the present study were obtained between December 8, 2005, and September 30, 2011. Fifty-six non-treatment-seeking CUs who met at least 1 of the DSM-IV-TR substance dependence criteria 3 to 7 and 56 HCs participated. The groups were carefully matched on age, sex, years of formal education, race, Wechsler Adult Intelligence Scale Vocabulary score, and smoking status. None had any major illness or history of neuropsychiatric disorders other than current abuse/dependence on cocaine, nicotine, or both. On the day of scanning, participants were assessed for recent alcohol use with breath sample testing and for other recent drug use with a urine drug screen. Participants with a positive breath sample test result were rescheduled or discharged from the study. This study was approved by the Institute Review Board of the National Institutes of Health. Written informed consent was obtained from all individuals prior to study enrollment, and participants received financial compensation.
Assessment of Impulsivity and Loss of Control Over Cocaine Use

The BIS-11 was administered to 23 HCs and 24 CUs. The BIS-11 total score and subscale scores (Attention, Motor, and Non-planning) were used as regressors in subsequent functional connectivity analyses, as described below.

Five of the 7 DSM-IV-TR criteria of drug dependence (all but tolerance and withdrawal) reflect loss of control over substance use. In keeping with the DSM-5 use of number of criteria met as a measure of severity, we used the total number of these criteria met as a measure of individual severity of loss of control over drug use.

Seeds Selection and First-Level Functional Connectivity Computation

Six-minute resting functional magnetic resonance imaging data were collected and processed with standard procedures. Seed-based rsFC analyses were performed by placing bilateral 4-mm-radius spherical seeds within 6 a priori defined subdivisions of the striatum22–32,34: VS inferior and superior parts (VSi and VSs, respectively), dorsal caudate (DC), ventral rostral putamen (VRP), dorsal rostral putamen (DRP), and dorsal caudal putamen (DCP) (eFigure 1 in the Supplement). The correlation coefficients (r) were then transformed using Fisher r to z transformation using the following equation:

\[ z = 0.5 \cdot \log \frac{1 + r}{1 - r} \]

The resultant z maps were defined as rsFC maps.

Statistical Analysis

The rsFC results for each bilateral pair of seeds with the rest of the brain were submitted to a 2 × 2 (hemisphere × group) mixed-design analysis of variance with age and head motion (the average framewise displacement; eMethods in the Supplement) included as covariates, masked by an or map of significant connectivity for each bilateral seed in each group (ie, left seed [CU] or right seed [CU] or left seed [HC] or right seed [HC]). Multiple comparison correction (corrected P < .05) was determined at the cluster level based on Monte Carlo simulations.35 Further details regarding participants, data acquisition, preprocessing, head motion correction, and spatial constraints at the group-level analysis are presented in the eMethods in the Supplement.

Associations Between Striatal rsFC and Self-report Assessments

The mean rsFC within regions of interest resulting from the group-level analysis of variance were regressed against years of cocaine use, current use (the mean amount of money spent per week on cocaine in the past month), BIS-11 total scores, and the 3 BIS-11 subscale scores, with age and head motion used as covariates.

Correlations between loss of control over cocaine use and the coupling between potential combinations of VS-aPFC/OFC (go) and VS-dACC (stop) circuits showing between-group differences were examined and corrected for multiple comparisons to test our second hypothesis.

Results

Demography and Behavior

The CU and HC participants were well matched for age, educational level, sex, IQ, race, and cigarette smoking history. Years of cocaine use correlated with age (r = 0.48, P < .001). Compared with the HC group, the CU group showed significantly higher impulsivity as reflected by BIS-11 total and 3 subscales scores. The CU group showed a mean (SD) of 4.06 (1.29) of 5.0 possible cocaine compulsive-like symptoms. Fifty-two participants met criteria for DSM-IV-TR cocaine dependence, 3 met criteria for DSM-IV-TR cocaine abuse, and 1 met 1 loss-of-control criterion. Thirty-two CUs presented with negative and 23 with positive urine test results for cocaine. The Table summarizes the demographic and drug use history for all participants.

General Patterns of Striatal rsFC

Generally, both groups showed similar spatial topography patterns of rsFC with each of the 6 bilateral striatal seeds (eFigure 2 in the Supplement), which are similar to patterns previously reported.32 Briefly, the VSi showed significant connectivity to ventral mPFC and ventral OFC, the connectivity maps of VSs shifted to more superior mPFC and more lateral aPFC, and the connectivity maps of the DC included further superior mPFC and DLPFC. All seeds in the putamen showed significant functional connectivity to bilateral insula and similar inferior to superior prefrontal patterns going from ventral to dorsal seeds.

Analysis of Variance Results

In general, the striatal-cingulate, -insula, and -striatum connectivity strength was decreased, whereas the striatal-frontal connectivity was increased in the CUs compared with the HC group (eTable 1 in the Supplement and Figure 1). Specifically, the CU group demonstrated a significant reduction in rsFC strength between the VSi seed and the dACC and the superior temporal gyrus (Figure 1A) and between the VS seed and the dACC and the ventral part of striatum (Figure 1B). In contrast, the CU group showed increased rsFC strength between the DC and bilateral DLPFC (Figure 1C). For seeds in the putamen, the CU group demonstrated decreased connectivity strength within the DS, and with the cingulate and insula (Figure 1D-F). Connectivity strength between the DRP and occipital cortex was less negative in the CU group (Figure 1D). Analysis of variance revealed group × hemisphere interactions in several striatal networks, including VSs-aPFC/OFC, VRP-middle frontal gyrus, DCP-middle cingulate cortex, and DCP-hippocampus (eTable 1 in the Supplement and Figure 2). Circuits within the CU group did not differ significantly as a function of positive or negative urine screen on the day of scanning (eResults in the Supplement).

Associations Between Striatal rsFC and Self-report Assessments

Connectivity strength between the right DC and bilateral DLPFC predicted current cocaine use (P < .046; Figure 3). The connectivity strength of these 2 DC circuits also predicted the BIS-11 total scores in the CU group (P < .012; Figure 3). In addition, the right DC-right DLPFC circuit positively correlated with At-
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Original Investigation Research

dicted OFC and right VSi–dACC significantly and positively pre-
connectivity strength difference between right VSs–left aPFC/OFC circuit combinations to be tested in our model. We found that there were significantly different in the CU cohort, resulting in VS-dACC circuits (bilateral VSi-dACC and bilateral VSs-dACC) revealed 1 VS-aPFC/OFC circuit (right VSs–left aPFC/OFC) and 4 our measure of severity of loss of control over drug use re-
estimated in the present study is consistent with that in previous reports.\textsuperscript{2,38-40} A preponderance of evidence suggests that impul-
sivity (as measured by the BIS-11) likely both predisposes to co-
caine use and, in turn, is worsened by use.\textsuperscript{1,41,42} The neural sub-

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HC Group (n = 56)</th>
<th>CU Group (n = 56)</th>
<th>Difference</th>
<th>P Value</th>
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<td>Sex, No. (%)</td>
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<td>Age, mean (SD), y</td>
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<td>39.86 (6.71)</td>
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<td>.40</td>
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<td>Formal education, mean (SD), y</td>
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<td>12.87 (1.36)</td>
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<td>.23</td>
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<td>54.66 (8.97)</td>
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<td>Nonsmoker</td>
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<td>18 (32)</td>
<td>$\chi^2 = 1.39$</td>
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<td>10-19</td>
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<td>≥20</td>
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<td>11 (20)</td>
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<td>Mixed</td>
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<td>Cocaine use assessment, mean (SD)</td>
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<td>Duration, y</td>
<td>12.64 (6.40)</td>
<td>246.70 (168.94)</td>
<td>$t = -4.58$</td>
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<td>Current use, $/wk</td>
<td>4.50 (1.58)</td>
<td>3.46 (1.29)</td>
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<td>Severity of loss control over drug use$^{a}$</td>
<td>3.46 (1.29)</td>
<td>3.46 (1.29)</td>
<td>$t = 0.08$</td>
<td>.28</td>
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<td>Cocaine urine test result, No. (%)</td>
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<td>Positive</td>
<td>23 (41)</td>
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<tr>
<td>fMRI motion, mean (SD)</td>
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<tr>
<td>FD</td>
<td>0.15 (0.09)</td>
<td>0.13 (0.08)</td>
<td>$t = 1.08$</td>
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<td>Censoring rate$^{c}$</td>
<td>0.02 (0.05)</td>
<td>0.02 (0.05)</td>
<td>$t = 0.32$</td>
<td>.75</td>
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<td>BIS-11 score, mean (SD)$^{d}$</td>
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<td>67.33 (10.30)</td>
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<td>Attention</td>
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<td>15.13 (3.64)</td>
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<td>.009</td>
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<td>Motor</td>
<td>20.50 (2.81)</td>
<td>24.92 (5.00)</td>
<td>$t = -3.77$</td>
<td>.001</td>
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<td>Nonplanning</td>
<td>21.17 (5.64)</td>
<td>27.29 (4.22)</td>
<td>$t = -4.23$</td>
<td>.001</td>
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</table>

Abbreviations: BIS-11, Barratt Impulsiveness Scale, version 11; CU, cocaine user; FD, frame displacement; fMRI, functional magnetic resonance imaging; HC, healthy control; WAIS, Wechsler Adult Intelligence Scale.

$^{a}$ Drug dependence is defined as the number of the 7 questions responded to by the participant during the DSM-IV-TR clinical interview.

$^{b}$ Severity of loss control over drug use is defined as the number of the 5 questions (excluding withdrawal and tolerance) responded to by the participant during the DSM-IV-TR clinical interview.

$^{c}$ Censoring rate is defined as the ratio between censored time points and total time points.

$^{d}$ The BIS-11 test was conducted in 23 HCs and 24 CUs.

Discussion

Corticostriatal interactions have been suggested to be crucial for computing reward, decision making, motivation, and habit learning.\textsuperscript{3,15,36-37} Using resting-state functional magnetic resonance imaging, we observed altered striatal functional connectivity in the CU group compared with a well-matched HC group. Increased striatal-DLPPC connectivity strength was positively correlated with recent cocaine use and elevated BIS-11 impulsivity scores, and the difference between striatal–dACC and striatal–aPFC/OFC connectivity strength was associated with the number of DSM-IV-TR substance dependence loss-of-control criteria met. The elevated trait impulsivity in CU vs HC participants found in the present study is consistent with that in previous reports.\textsuperscript{2,38-40} A preponderance of evidence suggests that impulsivity (as measured by the BIS-11) likely both predisposes to cocaine use and, in turn, is worsened by use.\textsuperscript{1,41,42} The neural sub-
strate underlying this impulsivity in CUs has, to our knowledge, not been well established. A morphometric study revealed a positive correlation between impulsivity and caudate volume. Since the caudate receives dense projections from DLPFC, the correlation found between BIS-11 demonstrated impulsivity and the DC-DLPFC connectivity is highly relevant to this finding. The increased DC-DLPFC rsFC, which was also correlated with current cocaine use, was correlated with impulsivity only in CUs. This observation could be pointing to a mechanism for increased impulsivity due to cocaine use or it could reflect a neural basis for impulsivity that is premorbid but different from the neural basis for impulsivity in the general population. Impulsivity is a multifaceted construct. The BIS-11 and laboratory tasks, such as delay discounting with cocaine (which directly relates...
to drug use), or tasks requiring inhibition of prepotent motor responses, may capture different dimensions of impulsivity, which is supported by both distinct phenotypes revealed by factor analysis and the absent or weak correlation between them. The neural correlates of BIS-11 demonstrated impulsivity in CUs observed in the present study may not necessarily subserve other aspects of impulsivity. Indeed, it did not correlate with the VS-dACC circuit that we believe may reflect inhibitory control.
problems related to addiction. However, using a measure of impulsivity that is not cocaine specific allows us to explore a feature commonly associated with but not defining cocaine dependence in a way that captures results that may relate to preexisting impulsivity, impulsivity resulting from cocaine use, or their combination.

Although drug addiction and OCD are regarded as distinct disorders, they share compulsive phenotypic characteristics, and the co-occurrence of substance dependence in OCD is higher than that in many other neuropsychiatric disorders. It is thus mechanistically plausible that these 2 disorders also share neural substrates underlying their common phenotypic characteristics. Increased rsFC between striatum and frontal cortex has been repeatedly observed in patients with OCD, with positive correlation to disease severity. Similarly, we identified increased frontostriatal connectivity in the CU participants (e.g., rVSS-aPFC/OFC) (Figure 2), which was marginally positively correlated with loss of control over cocaine use, possibly reflecting an irresistible urge to use cocaine despite adverse consequences that has parallels to compulsions in OCD. This suggests that such frontostriatal network dysregulation may be a common neural substrate underlying compulsive behaviors in both OCD and drug abuse.

In this cocaine-using population, we replicated the ventral striatal-dACC circuit that was previously found to be reduced in smokers and negatively correlated with severity of nicotine dependence and found it also to be negatively correlated with a measure of severity of cocaine dependence, the number of loss-of-control criteria met. This replication suggests that this circuit has a similar pattern of abnormality in cocaine users as in smokers and may therefore represent a circuit abnormality common to stimulant addictions. Furthermore, we found decreased striatal-dACC circuit strength from other striatal seeds as well as reduced striatal-striatum connectivity in both ventral and dorsal striatal networks in CUs (Figure 1). The dACC projects to virtually the entire striatum while the ventral and dorsal portions are connected to each other by spiral interprojection loops. In line with this structural profile, functional connectivity studies, including the present, demonstrate connectivity between the dACC and the entire striatum, suggesting the possibility that information flowing through the striatum is likely modulated by dACC input. Congruent with this idea, the dACC has been implicated in diverse functions including reward-related decision making, conflict monitoring, and error accuracy. Thus, decreased connectivity between the dACC and striatum in CU participants in the present study may result from or partially reflect dACC hypoactivity seen in drug users performing inhibitory control tasks. Notably, error-related dACC hypoactivity predicts cocaine relapse and error-related dACC hyperactivity is seen in successful long-term cocaine abstinence. Based on these findings, we speculate that decreased striatal-dACC connectivity may serve as a neural substrate of impaired error awareness and reduced cognitive regulation over drug use.

The relationship between resting-state connectivity, behavioral performance, and clinical predictors is an area of active investigation. A growing number of studies have demonstrated that the connectivity strength of circuits at rest predicts both the activation of those same circuits during task performance as well as the subsequent behavioral performance relative to that circuit. Of relevance to this study, we have previously demonstrated that the interactions between several resting-state circuits/networks (salience, default-mode, and executive-control) predict acute nicotine abstinence effects on craving and cognitive function.

In the present study, we tested the hypothesis that drug addiction can result from a disruption of a balance between go and stop processes that support appropriate responses to the environment. Understanding the neural substrates underlying these processes is a critical step in the development of more
efficacious neurobiologically based treatments. The combined connectivity strength metric we created based on VS-aPFC/OFC and the VS-dACC circuits significantly correlated with DSM-IV-TR-based characteristics of loss of control over drug use (Figure 4). We posit that increased VS-aPFC/OFC and decreased VS-dACC connectivity strength in cocaine users may reflect strengthened compulsive go processes coupled with impaired regulatory stop processes. Clinically, it has been proposed that either reversing the maladaptive go processes or enhancing the stop processes may be an effective intervention strategy.63 Indeed, deep-brain stimulation of the striatum in patients with OCD restores excessive striatal-aPFC/OFC rsFC and is accompanied by relief of disease symptoms.64 Given similar compulsivity between drug addiction and OCD, it is an open question whether restoration of the excessive go circuit (striatal-aPFC/OFC) connectivity strength identified will reduce compulsive behaviors in some cocaine users. Rescuing cocaine-induced PFChypoactivity using optogenetic stimulation prevents compulsive drug seeking in rats.62 In human studies, electrical stimulation of dACC induces a strong will to persevere in the face of challenges,63 while dACC hyperactivity is seen in long-term cocaine abstinence.29 Based on these findings, strengthening the stop circuit (striatal-dACC) hypoconnectivity in drug users by cognitive training and/or electrical stimulation may enhance an individual’s ability to resist further drug use. More interestingly, stronger correlation between drug compulsivity and go (→) stop coupling than between go or stop circuits alone would suggest that a dual therapeutic intervention aimed at reversing these maladaptive go processes coupled with enhancing impaired stop processes may be more efficacious than a single target strategy, and identifying individual variations in go and stop dysfunction may guide individualized treatment strategies.

Like all such studies, ours has several limitations. As a cross-sectional design, our data cannot speak to the causal relationship between neural imaging measurements and addiction related behaviors/traits. Although the present study revealed altered striatal networks and their relationship with impulsivity and loss of control over drug use in CUs, various behavioral tasks measuring constructs previously associated with cocaine dependence (eg, delay discounting for impulsivity, reversal learning for cognitive flexibility, and their relationship with identified striatal networks in drug users) could help to better understand the clinical relevance of the present work. More men than women participated in the study, which limits investigation of sex-specific striatal circuit abnormality. Finally, we did not use multiple comparison corrections when exploring the relationship between resting circuit strength, drug use behaviors, and BIS-11 measures, requiring replication of these findings.

Conclusions

To our knowledge, the present data represent the first identification of discrete striatal-cortical circuits associated with key addiction phenotypic characteristics. Combining discrete striatal-cortical circuits that are associated with key addiction phenotypic characteristics may provide novel insight into treatment.


