OXFORD

International Journal of Neuropsychopharmacology (2023) 26: 627–638

https://doi.org/10.1093/ijnp/pyac019
Advance Access Publication: August 14, 2023
Regular Research Article

REGULAR RESEARCH ARTICLE

Resting-State Functional Connectivity of the Dorsal and Ventral Striatum, Impulsivity, and Severity of Use in Recently Abstinent Cocaine-Dependent Individuals

Xue Dong, Simon Zhornitsky, Wuyi Wang, Thang M. Le, Yu Chen, Shefali Chaudhary, Chiang-Shan R. Li, Sheng Zhang

Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut, USA (Ms Dong, Drs Zhornitsky, Wang, Le, Chen, Chaudhary, Li, and Zhang); Department of Psychology, Youth Mental Health Education Center, Shaanxi University of Science & Technology, Xian, Shaanxi, China (Ms Dong); Department of Neuroscience, Yale University School of Medicine, New Haven, Connecticut, USA (Dr Li); Interdepartmental Neuroscience Program, Yale University, New Haven, Connecticut, USA (Dr Li); Wu Tsai Institute, Yale University, New Haven, Connecticut, USA (Dr Li).

Correspondence: Sheng Zhang, PhD, Connecticut Mental Health Center, S103, 34 Park Street, 06519-1109 New Haven, CT, USA (sheng.zhang@yale.edu).

Abstract

Background: Previous studies have focused on both ventral striatum (VS) and dorsal striatum (DS) in characterizing dopaminergic deficits in addiction. Animal studies suggest VS and DS dysfunction each in association with impulsive and compulsive cocaine use during early and later stages of addiction. However, few human studies have aimed to distinguish the roles of VS and DS dysfunction in cocaine misuse.
Methods: We examined VS and DS resting-state functional connectivity (rsFC) of 122 recently abstinent cocaine-dependent individuals (CDs) and 122 healthy controls (HCs) in 2 separate cohorts. We followed published routines in imaging data analyses and evaluated the results at a corrected threshold with age, sex, years of drinking, and smoking accounted for.
Results: CDs relative to HCs showed higher VS rsFC with the left inferior frontal cortex (IFC), lower VS rsFC with the hippocampus, and higher DS rsFC with the left orbitofrontal cortex. Region-of-interest analyses confirmed the findings in the 2 cohorts examined separately. In CDs, VS-left IFC and VS-hippocampus connectivity was positively and negatively correlated with average monthly cocaine use in the prior year, respectively. In the second cohort where participants were assessed with the Barratt Impulsivity Scale (BIS-11), VS-left IFC and VS-hippocampus connectivity was also positively and negatively correlated with BIS-11 scores in CDs. In contrast, DS-orbitofrontal cortex connectivity did not relate significantly to cocaine use metrics or BIS-11 scores.
Conclusion: These findings associate VS rsFC with impulsivity and the severity of recent cocaine use. How DS connectivity partakes in cocaine misuse remains to be investigated.

Keywords: Cocaine addiction, brain imaging, resting-state functional connectivity, striatum, impulsivity

Received: December 8, 2021; **Revised:** February 3, 2022; **Accepted:** March 1, 2022

Significance Statement

Striatal circuit dysfunction is central to the pathophysiology of drug addiction. We aimed to contrast the roles of resting-state functional connectivity (rsFC) of ventral (VS) and dorsal (DS) striatum in cocaine misuse. In 2 cohorts of a total of 122 cocaine-dependent individuals (CDs) vs 122 healthy controls (HCs), we showed higher VS rsFC with the left inferior frontal cortex (IFC), lower VS rsFC with the hippocampus, and higher DS rsFC with the left orbitofrontal cortex (OFC). In CDs, VS-left IFC and VS-hippocampus connectivity was positively and negatively correlated with average monthly cocaine use, respectively. VS-left IFC and VS-hippocampus connectivity was also positively and negatively correlated with impulsivity in CDs, respectively. In contrast, DS-OFC connectivity did not relate significantly to the severity of cocaine use or impulsivity. These findings associated VS but not DS rsFC with impulsivity and the severity of recent cocaine use in abstinent chronic cocaine users.

Introduction

Cocaine addiction is a chronic, relapsing illness characterized by motivation dysfunction. It is posited that cocaine-dependent individuals respond less to natural reinforcers and engage instead in habitual drug-seeking and consumption (Knackstedt et al., 2014). Extensive evidence implicates the dopaminergic circuits in uncontrolled cocaine use (Volkow et al., 2011; Cachope and Cheer, 2014). Both the ventral striatum (VS) and dorsal striatum (DS) receive dopaminergic inputs from the ventral tegmental area and substantia nigra, pars compacta (Alexander et al., 1986), and support reward and habit learning and other behaviors associated with drug abuse (Volkow et al., 2011; Ersche et al., 2020; Ersche et al., 2021; Lim et al., 2021).

Imaging studies have characterized dopaminergic deficits (Volkow et al., 2006; Wong et al., 2006; Martinez et al., 2007; Volkow et al., 2011) and described altered VS and DS activation during cognitive challenges in individuals with drug addiction, including cocaine addiction (Cisler et al., 2013; Ding and Lee, 2013; Konova et al., 2013; Vaquero et al., 2017; Zhang and Li, 2018). For instance, cocaine-dependent individuals (CDs) relative to healthy controls (HCs) exhibited higher VS activation during wins vs losses in a lottery task (Vaquero et al., 2017). Using positron emission tomography, studies showed that dopamine in the DS but not in the VS was positively correlated with self-reports of cocaine craving in CDs (Volkow et al., 2006; Wong et al., 2006). Another study observed higher striatal-frontal and lower striatal-insula and cingulate resting-state functional connectivity (rsFC) in non–treatment-seeking CDs compared with HCs. Further, striatal-frontal connectivity strength was positively correlated with the severity of recent cocaine use and elevated trait impulsivity in CDs (Hu et al., 2015). Besides cocaine addiction, a more recent work reported higher DS-orbitofrontal cortex (OFC) rsFC in multiple substance users with high vs low misuse severity (Oh et al., 2020). Higher medial OFC activity was accompanied by stronger DS connectivity during negative emotional processing as well as rsFC in individuals with marijuana dependence (Zimmermann et al., 2018). These studies suggest both VS and DS dysfunction in association with impulsive and compulsive cocaine use during early and later stages of addiction.

A substantial number of studies provided evidence in support of differentiable roles of the VS and DS in cocaine misuse. Whereas the VS is involved in salience signaling and initial learning of goal-directed behavior (Atallah et al., 2014), the DS mediates the transition to habitual, stimulus-controlled behavior (Smith and Graybiel, 2013). Thus, previous studies have posited a role of the VS and DS during the early and later stages of addiction when individuals engage in impulsive and compulsive drug use, respectively. The hypothesis has been investigated mostly in animals engaged in reward-related behavior and/or drug use (McClure et al., 2004; Dalley et al., 2007; Behan et al., 2015; Everitt and Robbins, 2016; Pascoli et al., 2018; Luscher et al., 2020). For instance, impulsive animals showed markedly reduced fallypride binding after haloperidol vs saline treatment—suggesting greater reduction in dopamine $D_{2/3}$ receptors—within the VS but not DS (Mukherjee et al., 1999), with the reduction of VS $D_{2/3}$ receptor binding correlated with impulsivity on a 5-choice serial reaction time task (Dalley et al., 2007). Other studies implicated the DS in the progressesion from goal-directed to habitual cue-induced drug taking (Everitt and Robbins, 2005, 2016), a shift partly independent from impulsivity-driven drug use (Murray et al., 2014). Cue-evoked dopamine release was observed in the DS when substance use became compulsive (Ito et al., 2002), and dopamine receptor blockade in the DS but not VS reduced cocaine-seeking behavior (Vanderschuren et al., 2005). The DS mediates compulsive drug seeking, and the association between DS dopaminergic activity and cue-induced craving may reflect the automatized nature of craving in cocaine addiction (White, 1989; Tiffany, 1990; Porrino et al., 2004; Sinha et al., 2005; Vanderschuren et al., 2005). These findings have suggested different roles of VS and DS circuit dysfunction in the transition from impulsive to compulsive drug use. Other studies contrasted VS and DS circuit dysfunction in cannabis misuse (Zhou et al., 2018), internet gaming addiction (Dong et al., 2021), and obesity (Contreras-Rodriguez et al., 2017). Indeed, shifts in VS-DS function and dysfunction have recently been examined in humans with cocaine (Hu et al., 2015), cannabis (Zhou et al., 2018), and internet gaming addiction (Dong et al., 2021) as well as those with obesity (Contreras-Rodriguez et al., 2017).

RsFC characterizes the functional architecture of the brain (Fox and Raichle, 2007; Gu et al., 2010; Hu et al., 2015; Zhang and Li, 2018). Numerous studies have described altered cortical and subcortical rsFC in addiction (Gu et al., 2010; Kelly et al., 2011; Sutherland et al., 2012; Zhang et al., 2016, 2017; Gawrysiak et al., 2017; Zhang and Li, 2018). However, other than Hu et al. (2015), as discussed further later, no studies to our knowledge have examined VS/DS rsFC in cocaine addiction. Here, we investigated the rsFC of the VS and DS in CDs compared with HCs in a relatively large sample of participants. We characterized the relationship between the connectivity measures and cocaine use variables as well as an impulsivity trait, with the goal to distinguish VS and DS dysfunction in cocaine misuse. On the basis of the literature, we hypothesized that VS and DS rsFC were each associated with impulsivity and the severity of recent cocaine use.

MATERIALS AND METHODS

Participants, Informed Consent, and Assessment

A total 122 recently abstinent participants with cocaine dependence (CDs, 95 men) and 122 age- and gender-matched

healthy control participants (HCs, 85 men) took part in the study (Table 1). The great majority of CDs (120 out of 122) smoked cocaine. CDs and HCs were recruited and studied with similar protocols over 2 study periods. The first (66 CDs and 66 HCs) and second (56 CDs and 56 HCs) cohorts were each scanned with a single- and multi-band magnetic resonance imaging (MRI) sequence in a protocol that involved resting-state before different task-based functional MRI (fMRI) scans.

CDs met the criteria for current cocaine dependence as diagnosed by the Structured Clinical Interview for DSM-IV (First et al., 1995). Recent cocaine use was confirmed by urine toxicology screens. Participants were drug-free while staying in an inpatient unit for 7 to 10 days prior to the current fMRI study. Smokers were allowed to smoke if they so wished until the fMRI scan to minimize the effect of nicotine craving in the current study and per our scan routines. All participants were physically healthy with no major medical illnesses or current use of prescription medications. None reported having a history of head injury or neurological illness. Other exclusion criteria included dependence on another psychoactive substance (except nicotine) and current or past history of psychotic disorders. The Human Investigation committee at Yale University School of Medicine approved all study procedures, and all participants signed an informed consent prior to the study.

For CDs, the following inclusion criteria were required for eligibility: (1) between 18 and 55 years old; (2) able to read and write; (3) meet DSM-IV criteria for cocaine dependence; report current cocaine use of once or more a week; confirmation of recent cocaine use in urine toxicology test during intake assessments and prior to admission to the Connecticut Mental Health Center; and (4) physically healthy with no major medical illnesses, current use of prescription medications, or history of head injury or any neurological illness. Other exclusion criteria included (1) current or past history of psychotic disorders; (2) current major depressive or anxiety disorders; (3) abuse or dependence on another substance, except nicotine and caffeine; (4) current use of any psychoactive drugs, including anxiolytics and antidepressants; (5) foreign ferromagnetic objects in the body or other MR contraindications (e.g., claustrophobia); and (6) pregnancy or lactation (women only).

CDs were evaluated for history of and recent cocaine use, with the average number of days of cocaine use in the prior month, average total monthly amount of cocaine use in the prior year, and years of cocaine use documented. Cocaine craving was assessed with the Cocaine Craving Questionnaire, brief version (CCQ-Brief), for CDs every 2 to 3 days during the inpatient stay (Sussner et al., 2006). The CCQ-Brief is a 10-item questionnaire abbreviated from the CCQ-Now (Tiffany et al., 1993). CCQ-Brief, CCQ-Now, and other measures were highly correlated in craving assessment (Sussner et al., 2006). Each item was rated on a scale from 1 to 7, with a higher total score (ranging from 10 to 70) indicating greater craving.

The Barratt Impulsivity Scale (BIS-11) (Patton et al., 1995) was administered to the multi-band cohort (see next section) of 56 CDs and 56 HCs. The BIS-11 total score and attention, motor, and non-planning subscale scores were used in regression analyses.

Imaging Protocol and Data Preprocessing

One 10-minute resting-state fMRI scan was obtained for both CDs and HCs with eyes closed but awake. Brain images of 66 CDs and 66 HCs were collected using single-band imaging with a 3-Tesla MR scanner (Siemens Trio, Erlangen, Germany) as in our previous study (Zhang and Li, 2018). Brain images of

Table 1. Demographics and Clinical Measures of the Participants

	CDs			HCs			*P* value				
							CDs vs HCs			SB vs MB	
	All (n = 122)	SB (n = 66)	MB (n = 56)	All (n = 122)	SB (n = 66)	MB (n = 56)	All (n = 122)	SB (n = 66)	MB (n = 56)	CDs	HCs
Age, y	43.1 ± 7.4	41.4 ± 7.3	45.2 ± 7.1	41.7 ± 8.8	39.1 ± 9.2	44.8 ± 7.2	.18	.13	.74	.004	<.001
Gender (M/F)	95/27	49/17	46/10	85/37	43/23	42/14	.19^	.26^	.36^	.29^	.24^
Years of drinking	19.9 ± 10.6	14.0 ± 7.2	26.9 ± 9.7	19.7 ± 11.4	14.4 ± 9.1	26.1 ± 10.5	.90	.78	.66	<.001	<.001
CCQ score	31.6 ± 17.2	23.8 ± 10.4	38.6 ± 17.2	N/A	N/A	N/A	N/A	N/A	N/A	<.001	N/A
Monthly cocaine use (average, prior year), g	29.9 ± 29.3	32.5 ± 30.9	26.7 ± 27.4	N/A	N/A	N/A	N/A	N/A	N/A	.28	N/A
Cocaine use (prior month), d	18.0 ± 8.6	17.1 ± 9.1	19.0 ± 7.8	N/A	N/A	N/A	N/A	N/A	N/A	.22	N/A
Cocaine use, y	18.4 ± 8.4	20.1 ± 7.2	16.3 ± 9.3	N/A	N/A	N/A	N/A	N/A	N/A	.012	N/A
BIS-11 total score	N/A	N/A	65.6 ± 10.9	N/A	N/A	54.9 ± 8.4	N/A	N/A	<.001	N/A	N/A
Attention subscore	N/A	N/A	16.2 ± 3.8	N/A	N/A	13.2 ± 2.9	N/A	N/A	.002	N/A	N/A
Motor subscore	N/A	N/A	20.5 ± 4.5	N/A	N/A	20.0 ± 3.4	N/A	N/A	.43	N/A	N/A
Nonplanning subscore	N/A	N/A	28.0 ± 6.8	N/A	N/A	21.7 ± 4.2	N/A	N/A	<.001	N/A	N/A

Abbreviations: CCQ, Cocaine Craving Questionnaire; All, single-band + multi-band sample; SB, single-band sample; MB, multi-band sample.
Values are mean ± SD; *P* values are based on 2-tailed 2-sample *t* test except for ^χ^2 test.

the second cohort (56 CDs and 56 HCs) were collected using multiband imaging with a 3-Tesla Siemens Trio scanner. Data were analyzed with Statistical Parametric Mapping (SPM8, Wellcome Department of Imaging Neuroscience, University College London, UK), and standard preprocessing and additional preprocessing of rsFC analysis was performed. Please see details in the supplement.

Head Motion

As extensively investigated in Van Dijk et al. (2012), micro head motion (>0.1 mm) represents an important source of spurious correlations in rsFC analysis (Van Dijk et al., 2012). Therefore, we applied "scrubbing" as in previous studies (Smyser et al., 2010; Power et al., 2012; Tomasi and Volkow, 2014) to remove time points affected by head motions. Briefly, for every time point t, we computed the framewise displacement given by $FD(t) = |\Delta d_x(t)| + |\Delta d_y(t)| + |\Delta d_z(t)| + |\Delta\alpha(t)| + |\Delta\beta(t)| + |\Delta\gamma(t)|$, where (d_x, d_y, d_z) and (α, β, γ) are the translational and rotational movements, respectively (Power et al., 2012). The second head movement metric was the root mean square variance (DVARS) of the differences in % blood oxygen level dependent (BOLD) intensity I(t) between consecutive time points across brain voxels, computed as follows: $VARS(t) = \sqrt{\langle |I(t) - I(t-1)|^2 \rangle}$, where the brackets indicate the mean across brain voxels. Finally, to compute each participant's correlation map, we removed time points with FD(t) > 0.5 mm or DVARS(t) >0.5% (Power et al., 2012; Tomasi and Volkow, 2014). On average, 1% of the time points were removed across participants.

Seed-Based Correlation and Group Analyses

We used the same VS mask as in our previous studies (Li et al., 2014; Zhang and Li, 2018). The DS mask was combined of the caudate, putamen, and pallidum templates from the Anatomical Automatic Labeling atlas (Tzourio-Mazoyer et al., 2002). A small number of voxels that overlapped between the 2 masks were removed (Fig. 1).

The BOLD time courses were averaged spatially for both the VS and DS mask. For individual participants, we computed the correlation coefficient between the averaged time course of each seed region and the time courses of all other brain voxels. To assess and compare the rsFC, we converted these image maps, which were not normally distributed, to z score maps by Fisher's z transform (Jenkins and Watts, 1968; Berry and Mielke, 2000): $z = 0.5\log_e\left[\frac{1+r}{1-r}\right]$. The Z maps were used in group random-effects analyses. We performed a 1-sample t test on the Z maps of both VS and DS for CDs and HCs and 2-sample t test with age, sex, and years of drinking as covariates to compare the 2 groups.

In region of interest (ROI) analysis, we used MarsBaR (http://marsbar.sourceforge.net/) to derive for each individual participant the functional connectivity z scores for the ROIs. Functional ROIs were defined based on "activated" clusters obtained from whole-brain analysis in the comparison of CDs and HCs and in the correlation with clinical metrics. All findings were presented in Montreal Neurological Institute (MNI) coordinates and brain regions identified with an atlas (Duvernoy, 1999).

In addition, we examined how well these rsFC features distinguished CDs from HCs. The accuracy was assessed using receiver operating characteristic (ROC) analysis, with the area under the curve (AUC) to indicate classification accuracy (Macmillan and Creelman, 2005; Zou et al., 2007). The ROC curve was created by plotting the true positive rate (sensitivity) against the false positive rate (1 – specificity) at various thresholds to distinguish CDs from HCs. Thus, the AUC considers both sensitivity and specificity and is a threshold-independent measure of classification performance.

RESULTS

Demographics and Clinical Measures

The demographic and clinical characteristics of the participants as well as the statistics are shown in Table 1. CDs and HCs did not differ in age, sex composition, or years of drinking in either single-band or multi-band sample or in the 2 samples combined. Both CDs and HCs were significantly older and had more years of drinking in the multi-band relative to single-band group. Further, CDs averaged 31.6 ± 17.2 in CCQ score across all assessments. Multi-band vs single-band CDs showed a higher CCQ score but fewer years of cocaine use. The 2 CD groups did not differ in average monthly cocaine use in the past year or days of cocaine use in the past week.

Participants in the multi-band sample were assessed with the BIS-11, and CDs relative to HCs showed higher BIS total score, inattention, and non-planning but not motor sub-score.

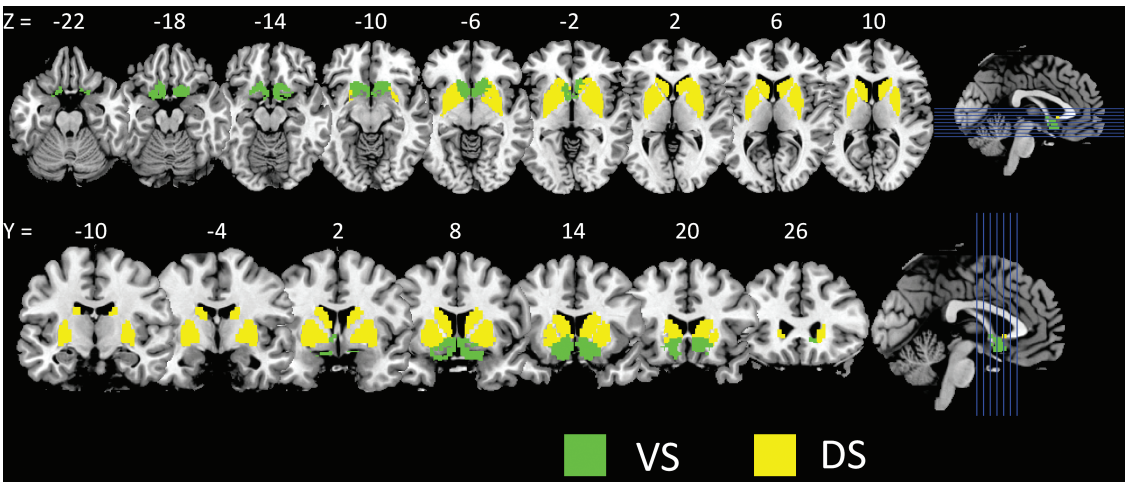

Figure 1. Seed regions: ventral (VS, green) and dorsal (DS, yellow) striatum are shown on axial (z = −22 to +10) and coronal (y = −10 to +26) sections of the brain.

rsFC

Examined at voxel $P<.05$ corrected for family-wise error on the basis of Gaussian random field theory, the results of a 1-sample t test of VS and DS rsFC with the whole brain are shown in supplementary Figure 1 for both CDs and HCs.

In a 2-sample t test with age, sex, and years of drinking as covariates, CDs relative to HCs showed higher VS rsFC with the left inferior frontal cortex (IFC), in the area of the inferior frontal sulcus, and lower VS rsFC with bilateral but predominantly right hippocampus at voxel $P<.001$ uncorrected and cluster-level $P<.05$ family-wise error. At the same threshold, CDs relative to HCs showed higher DS rsFC with the left lateral OFC in the area of the lateral orbital gyrus. These findings are shown in Figure 2 and the clusters are summarized in Table 2.

We compared CDs and HCs in the connectivity z scores of the ROIs (left IFC, bilateral hippocampus, and left OFC) separately for the single- and multi-band cohort with 2-sample t tests with age, sex, and years of drinking as covariates. The group differences were confirmed in both cohorts (supplementary Table 1). Further, CDs (mean ± SD = 16.6 ± 11.6) and HC (2.9 ± 7.0) showed significant difference in years of smoking ($P<.001$), and we included years of smoking as an additional covariate and re-examined group differences in rsFC for the multi-band data. The findings were largely identical (supplementary Table 1).

The ROC analysis showed that VS rsFC with the left IFC (AUC = 0.70) and with the hippocampus (AUC = 0.71) were slightly more accurate than DS rsFC with the left OFC (AUC = 0.67) in distinguishing the 2 groups (Figure 3).

Relationship of VS/DS rsFC to Clinical Characteristics

We evaluated the relationship between the rsFC and cocaine use variables—including CCQ score, average days of cocaine use in the prior month, average total monthly amount of cocaine use, and years of cocaine use—and age, sex, and years of drinking as covariates. Thus, with 3 ROIs and 4 cocaine use measures tested, the results of linear regression were evaluated with a corrected $P=.05/(4\times3)=.0042$. Across all 122 CDs, VS-left IFC and VS-hippocampus rsFC (z score) were each positively and negatively correlated with monthly cocaine use ($r=0.33$, $P=.00019$; $r=-0.35$, $P=.00007$), respectively. In contrast, DS-left OFC rsFC was not correlated with monthly cocaine use or any other cocaine use measures (all $Ps>.20$). To demonstrate differences in the correlation of VS and DS rsFC with monthly cocaine use, we also computed the rsFC z scores of DS-left IFC, DS-hippocampus, and VS-left OFC and compared the slopes of the regressions between VS and DS rsFCs. The results showed that VS- vs DS-left IFC ($z=2.85$, $P=.0044$) and VS- vs DS-hippocampus rsFC differed significantly ($z=-2.74$, $P=.0061$), but VS- vs DS-left OFC rsFC ($z=-0.7$, $P=.48$) did not differ significantly in the correlation with monthly cocaine use (Fig. 4).

The finding remained largely the same when the single- and multi- band participants were examined separately (supplementary Table 2). Participants in the multi-band cohort were evaluated with BIS-11. CDs showed higher total, inattention, and non-planning scores but not motor score compared with HCs (Table 1). Thus, we examined the relationship between VS/DS rsFC and BIS-11 total, inattention, and non-planning score with age, sex, and years of drinking as covariate (Fig. 5). Across the 56 CDs, the VS-left IFC rsFC z scores were positively correlated with BIS inattention ($r=0.30$, $P=.028$) and nonplanning ($r=0.33$, $P=.015$) subscores, and the VS-hippocampus rsFC strength was negatively correlated with BIS total score ($r=-0.28$, $P=.046$). All other VS rsFCs were not correlated with any of the BIS scores (all $Ps>.065$). No DS rsFC was correlated with BIS total or subscores (all $Ps>.35$).

Discussion

We observed higher VS rsFC with left IFC and lower VS rsFC with the hippocampus as well as higher DS rsFC with the left OFC in CDs compared with HCs. These rsFC features distinguished CDs from HCs with an accuracy of 70%–71%. (VS) and 67% (DS). The strength of VS but not DS rsFC with left IFC and with hippocampus was positively and negatively correlated with the severity of recent cocaine use, respectively. Further, VS but not DS rsFC with the left IFC and hippocampus were each positively and negatively associated with impulsivity, respectively. These findings together support a more prominent role of the VS than DS circuit dysfunction in reflecting both the severity of cocaine use and impulsivity in recently abstinent CDs who on average have been engaged in cocaine use for 18.4 years. We highlight some of the major findings below.

Altered VS and DS rsFC With the Frontal Cortex in Cocaine Addiction

The VS showed higher rsFC with the left IFC and the DS showed higher rsFC with the left OFC in CDs relative to HCs, consistent with previous findings of elevated striatal frontal cortical

Table 2. Regions Showing Differences in rsFC of VS and DS Between CDs and HCs

Volume	Peak voxel	MNI coordinate (mm)				
mm^3	Z	x	y	z	Side	Identified brain region
VS						
CDs > HCs						
5805	4.13	−21	41	16	L	Inferior frontal cortex
HCs > CDs						
3510	3.91	30	−25	−11	R	Hippocampus
DS						
CDs > HCs						
3753	4.48	−42	32	−2	L	Orbitofrontal cortex
HCs > CDs						
None						

Abbreviations: DS, dorsal striatum; L, left; R, right; VS, ventral striatum.
Voxel $P<.001$ and cluster-level $P<.05$, family-wise error.

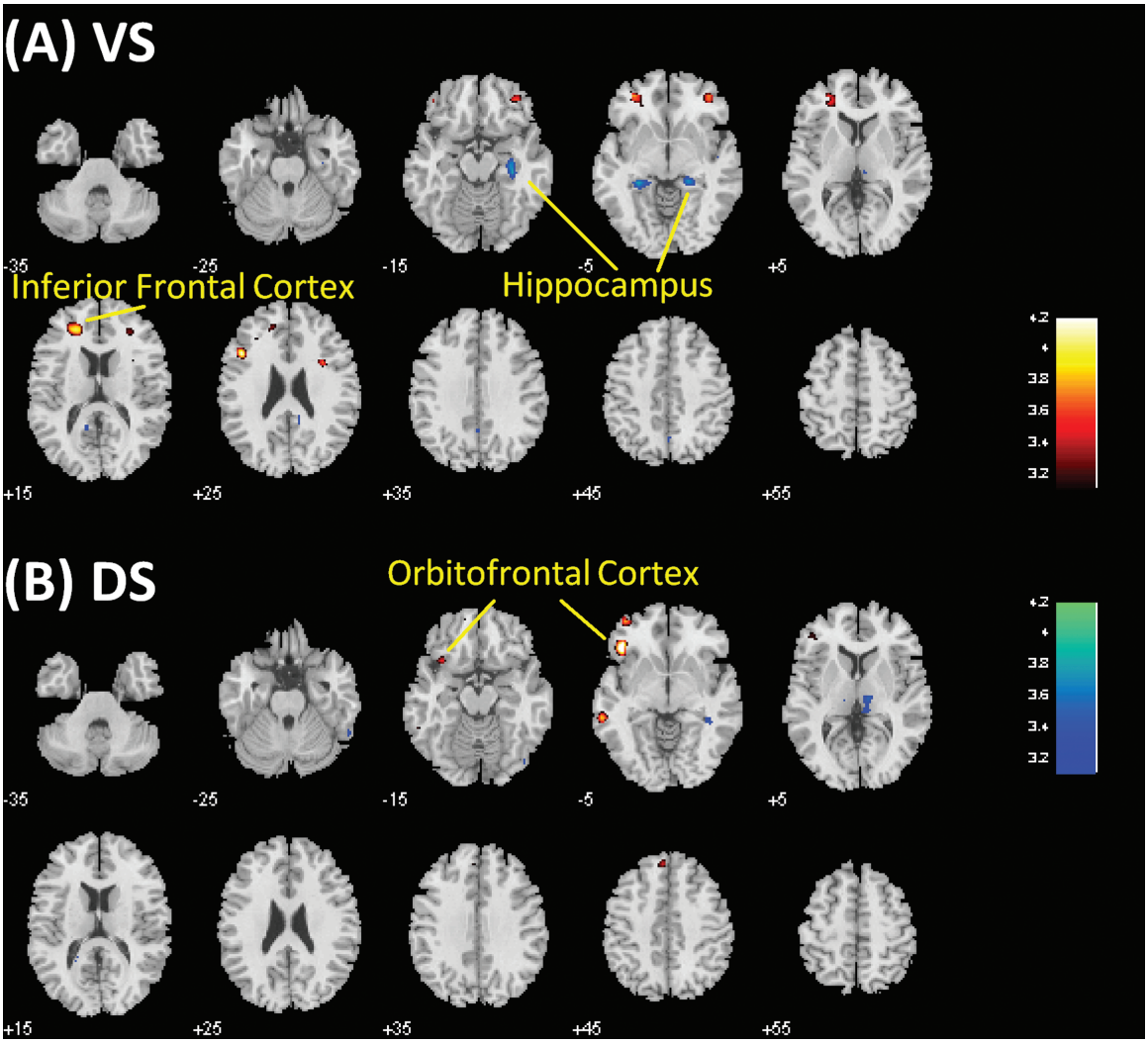

Figure 2. Brain regions showing differences between CDs (n = 122) and HCs (n = 122) in ventral (VS) and dorsal (DS) striatal rsFC, evaluated at voxel $P < .001$ uncorrected and cluster $P < .05$ family-wise error-corrected. Warm and cool voxels each show higher and lower rsFC with the seed region in CDs vs HCs. Brain sections are shown in neurological orientation: right = right, and the color bars show voxel T values. rsFC, resting state functional connectivity.

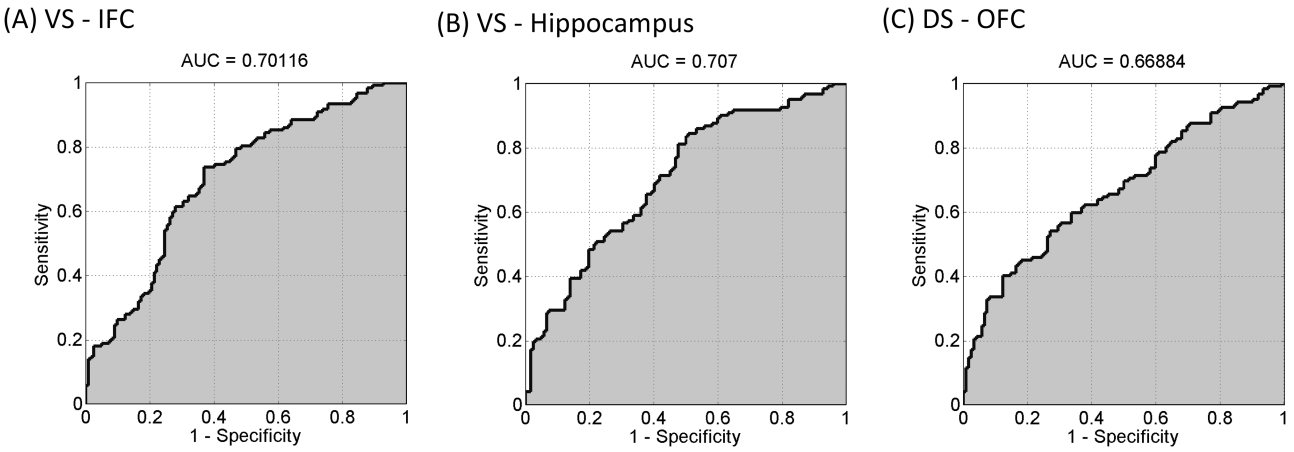

Figure 3. Receiver operating characteristic analysis showed that the VS rsFC with the left IFC (area under the curve or AUC = 0.70) and with the hippocampus (AUC = 0.71) were slightly more accurate than DS rsFC with the left OFC (AUC = 0.67) in distinguishing CDs and HCs. DS, dorsal striatum; IFC, inferior frontal cortex; OFC, orbitofrontal cortex; rsFC, resting state functional connectivity; VS, ventral striatum.

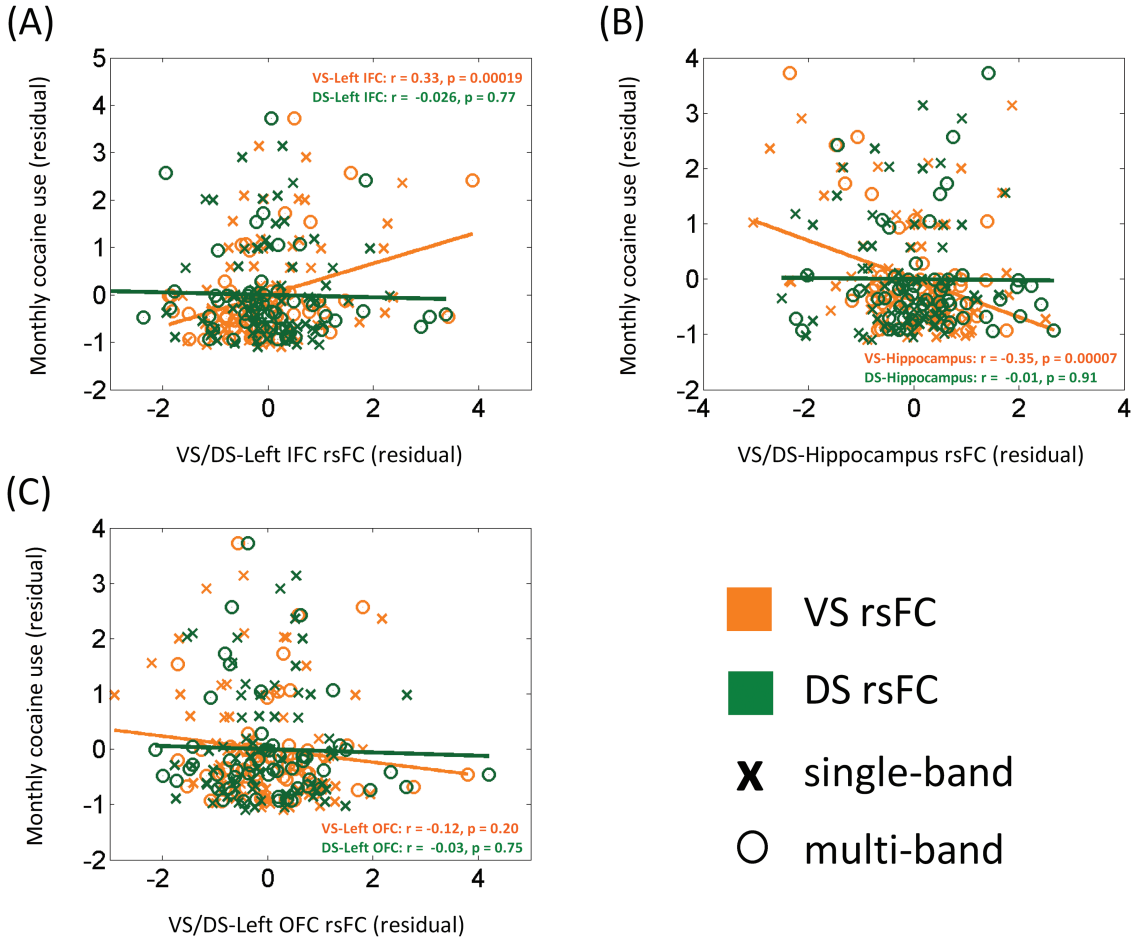

Figure 4. Linear regressions of VS/DS rsFC (z scores) of regions of interest vs average total monthly amount of cocaine use in the prior year, with age, sex, and years of drinking as covariates, in CDs. (A) VS/DS-left IFC. (B) VS/DS-hippocampus. (C) VS/DS-left OFC. Each data point represents the residual after accounting for age, sex, and years of drinking. Orange and green each show the data points and regression lines for the VS and DS. Crosses and circles represent participants from the single- and multi-band cohorts, respectively. DS, dorsal striatum; IFC, inferior frontal cortex; OFC, orbitofrontal cortex; rsFC, resting state functional connectivity; VS, ventral striatum.

connectivity (Hu et al., 2015; Zhang and Li, 2018). The IFC is part of the task control circuit disrupted in addiction (Volkow and Morales, 2015). Aberrant right IFC activation during emotion processing, decision-making, and inhibitory control has been reported in addicted individuals as well as recreational cocaine users (Goldstein and Volkow, 2011; Morein-Zamir et al., 2015; Canterberry et al., 2016; Zhukovsky et al., 2021). Cocaine relative to neutral cues evoked bilateral IFC activation in CDs (Tomasi et al., 2015). Reduction in D2 receptor signaling in the VS led to reduced IFC activity in individuals with addiction, gambling disorder, or obesity and has been associated with drug abuse and craving (Volkow and Baler, 2015). Both VS and right IFC showed positive correlation with craving rating during self-administration of cocaine in non–treatment-seeking CDs (Risinger et al., 2005), and both VS and bilateral IFC showed lower activation during decision-making in CDs who relapsed vs those who abstained during follow-ups (Stewart et al., 2014).

With an important role in learning, reward coding, and evaluation, and executive functions (Rolls and Baylis, 1994; Schoenbaum et al., 2006), the OFC is implicated in cocaine craving and behavioral disinhibition (Bonson et al., 2002; Burke et al., 2009; Wilcox et al., 2011; Moreno-Lopez et al., 2017; Zhang et al., 2020). The OFC receives projections from the ventral tegmental area and nucleus accumbens, subcortical targets for the reinforcing effects of addictive drugs (Walter et al., 2015). In humans, the OFC has reciprocal connections with many brain regions that process both primary and secondary rewards (Rolls, 2000). CDs relative to HCs showed greater activation in the right OFC during performance of the Iowa Gambling Task vs a control task (Bolla et al., 2003). Studies have also reported higher bilateral OFC activation in association with worse performance in controls but better performance in substance-abusing individuals in a Stroop task (Goldstein et al., 2001). In preclinical research, the resistance to punishment in cue-induced relapse was associated with enhanced OFC activity, while chemogenetic inhibition of the OFC reduced compulsive drug use (Pascoli et al., 2015). OFC dysfunction during odor discrimination reversal, reinforcement devaluation, and delay discounting was observed in rats undergoing withdrawal from cocaine use (Lucantonio et al., 2012).

The current findings of altered VS/DS-frontal cortical rsFC can be considered broadly with this literature. Whereas VS-left IFC connectivity was associated with impulsivity and the severity of cocaine use, the behavioral implications of these findings remain to be clarified.

Association of VS but Not DS rsFC With Impulsivity and Severity of Cocaine Use

The VS but not DS rsFC with the left IFC was associated with impulsivity and the severity of recent cocaine use. The VS has been consistently implicated in impulsivity (Basar et al., 2010;

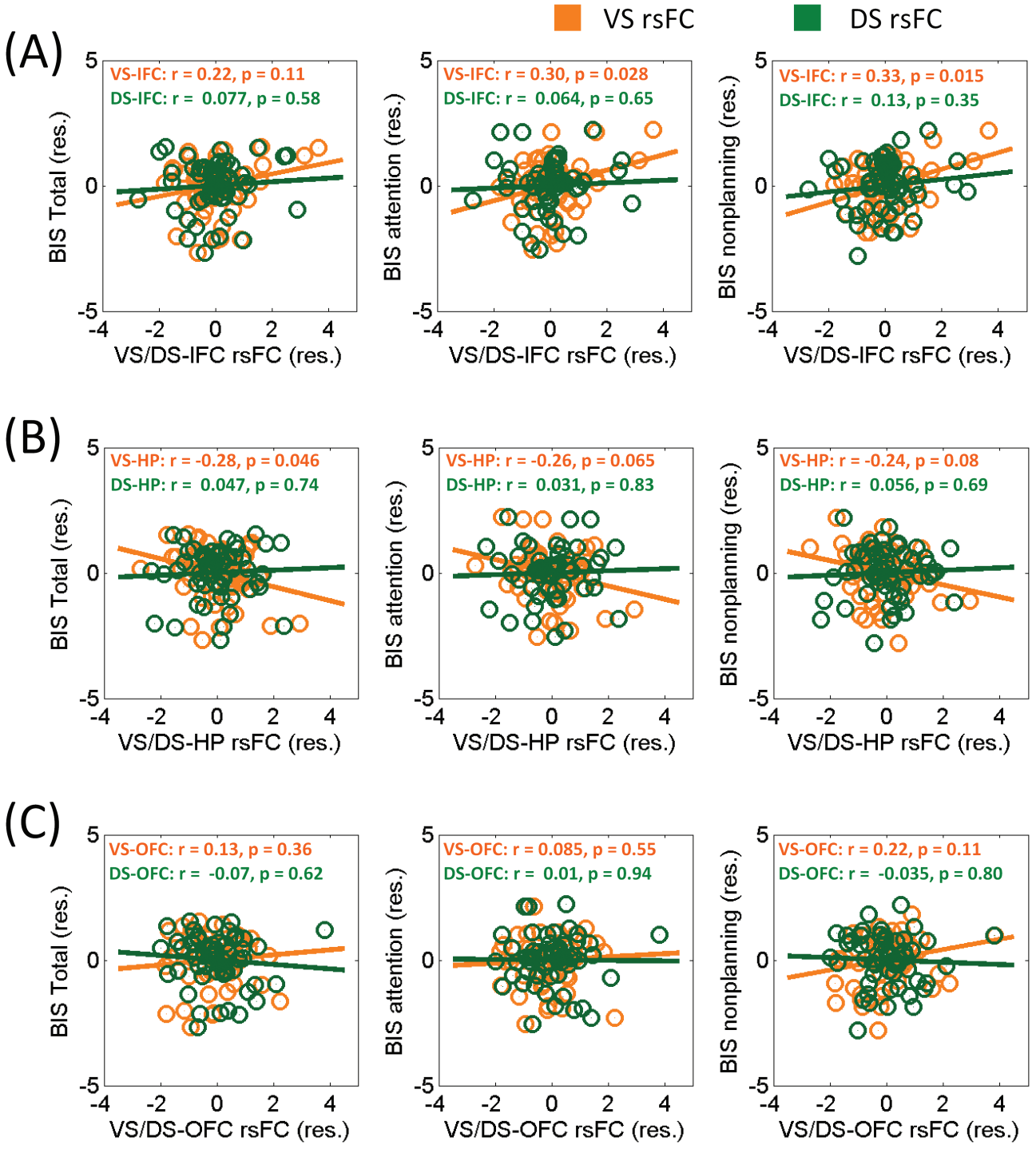

Figure 5. Linear regressions of VS/DS rsFC (z scores) of regions of interest vs BIS-11 total score, attention sub-score, and non-planning sub-score, with age, sex, and years of drinking as covariates, in CDs. (A) VS/DS-left IFC. (B) VS/DS-hippocampus. (C) VS/DS-left OFC. Each data point represents the residual after accounting for age, sex, and years of drinking. Orange and green each show the data points and regression lines for the VS and DS. DS, dorsal striatum; HP, hippocampus; IFC, inferior frontal cortex; OFC, orbitofrontal cortex; res, residual; rsFC, resting state functional connectivity; VS, ventral striatum.

Burton et al., 2015; Dalley and Robbins, 2017; Ide et al., 2020), and trait impulsivity was associated with higher gray matter volume of the left IFC in CDs (Moreno-Lopez et al., 2012). Animal studies suggested that IFC projections to the VS may drive impulsive activity (Robbins, 2007; Brewer and Potenza, 2008; Fineberg et al., 2010). On the other hand, the OFC-DS connectivity appeared to be instrumental to compulsive drug intake in rodents, as demonstrated by a loading pattern of intake, psychomotor sensitization, and responses for cocaine under a progressive ratio schedule of reinforcement (Minogianis et al., 2019). Consistent with the current finding, individuals abusing a variety of substances all showed elevated OFC-DS rsFC (Oh et al., 2020). More broadly, unmedicated patients with obsessive-compulsive disorder relative to HCs showed greater OFC-DS rsFC in positive

correlation with global symptom severity (Beucke et al., 2013). However, it remains unclear how exactly to characterize compulsive cocaine use in CDs. To the extent that the severity of compulsive cocaine use can be captured by years of cocaine use or quantity of cocaine use in the past year, we were not able to observe a significant relationship between DS rsFC and these cocaine use metrics.

Hu et al. (2015) examined the rsFC of VS and DS using six 4-mm-radius spherical seeds within the striatum in 56 non–treatment-seeking CDs and 56 HCs. The authors observed lower inferior VS-dorsal anterior cingulate and higher DS-dorsolateral prefrontal cortical connectivity in CDs vs HCs as well as an interaction effect in hemispherity for superior VS (VSs)-OFC connectivity. The DS-dorsolateral prefrontal cortical connectivity strength was positively correlated with current cocaine use and BIS-11 total scores. Further, the difference between inferior VS-dorsal anterior cingulate and VSs-OFC rsFC strength was positively correlated with DSM-IV-TR "compulsive" drug use symptoms, as reflected by the number of criterion symptoms endorsed other than withdrawal and tolerance. A number of issues are worth noting in comparing these and the current results. First, the VSs seed region (center coordinates: ±10, 15, 0) seemed to have most voxels within the DS in Hu et al. (2015). Second, it was not entirely clear whether the symptom severity metrics truly reflected compulsive drug use in Hu et al. (2015). One would argue that the symptom score better reflects the overall severity of cocaine addiction.

Altered VS rsFC With the Hippocampus in Cocaine Addiction

Compared with HCs, CDs showed lower VS rsFC with the hippocampus, consistent with our earlier finding of diminished rsFC of all 3 VS subregions, as defined by whole-brain connectivity parcellation, with bilateral hippocampi (Zhang and Li, 2018). The hippocampus showed higher activation to cocaine cues and cue-induced cocaine craving (Tomasi et al., 2015; Wang et al., 2021). Higher hippocampus regional blood flow and rsFC with the posterior cingulate cortex/precuneus predicted cocaine relapse (Adinoff et al., 2015). Exposure to cocaine cues induced dopamine release both in the VS and hippocampus in CDs (Fotros et al., 2013). In rats, repeated cocaine exposure potentiated hippocampal inputs to the VS (Muller et al., 2002; Britt et al., 2012; Pascoli et al., 2014), and withdrawal from cocaine administration led to attenuated long-term potentiation in the hippocampus–VS circuit (Goto and Grace, 2005). The latter findings mirror diminished VS-hippocampus connectivity, with greater diminution in link with the severity of recent cocaine use in our CDs, who were studied during early abstinence. Together, these preclinical and clinical studies suggest hippocampus–VS circuit dysfunction in cocaine addiction.

Limitations

A few limitations need to be considered. First, we documented years of smoking only for multi-band data, and CDs showed more years of smoking than HCs. Although we included years of smoking as a covariate in data analyses, we could not entirely rule out the effects of cigarette smoking on the current findings. Second, we did not have a specific measure of compulsory cocaine use in CDs. Thus, the current findings do not rule out the role of DS circuit dysfunction in compulsory cocaine consumption. More studies of cocaine use behavior and the psychological underpinnings of different patterns of cocaine use may help in advancing research on this important issue. In particular, longitudinal studies would provide vital information to document within-patient shifts of VS and DS dysfunction through the course of addiction. Third, our CDs were studied during early abstinence, and the current findings need to be considered as specific to this patient population. It remains to be seen whether and to what extent striatal rsFC may vary depending on the current state of cocaine use.

Conclusions

In conclusion, we explored rsFC of the VS and DS in cocaine addiction. CDs compared with HCs showed higher VS rsFC with the IFC and DS rsFC with the OFC as well as lower VS rsFC with the hippocampus. VS but not DS rsFCs were associated with cocaine use severity and impulsivity. These findings should be considered along with previous findings of a shift in activity from the VS to DS with the progression from impulsive to compulsive cocaine use (Hu et al., 2015). The findings highlight VS/DS circuit dysfunction as a neural marker of cocaine addiction and a more prominent role of VS circuit dysfunction in reflecting impulsivity and the severity of cocaine use.

Supplementary Materials

Supplementary data are available at *International Journal of Neuropsychopharmacology (IJNPPY)* online.

Acknowledgments

We thank the medical and nursing staff at the Clinical Neuroscience Research Unit, Connecticut Mental Health Center, for medical care of the participants.

This work was supported by National Institute on Drug Abuse at the National Institutes of Health (K25DA040032 and R21DA045743 to S. Zhang and R21DA044749 and R01DA023248 to C.R.L.) and the Department of Mental Health and Addiction Services of the State of Connecticut. The funding agencies otherwise had no role in the conceptualization of the study, data collection and analysis, or the decision to publish these results.

Interest Statement

The authors declare that they have no conflict of interest.

References

Adinoff B, Gu H, Merrick C, McHugh M, Jeon-Slaughter H, Lu H, Yang Y, Stein EA (2015) Basal hippocampal activity and its functional connectivity predicts cocaine relapse. Biol Psychiatry 78:496–504.

Alexander GE, DeLong MR, Strick PL (1986) Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci 9:357–381.

Atallah HE, McCool AD, Howe MW, Graybiel AM (2014) Neurons in the ventral striatum exhibit cell-type-specific representations of outcome during learning. Neuron 82:1145–1156.

Basar K, Sesia T, Groenewegen H, Steinbusch HWM, Visser-Vandewalle V, Temel Y (2010) Nucleus accumbens and impulsivity. Prog Neurobiol 92:533–557.

Behan B, Stone A, Garavan H (2015) Right prefrontal and ventral striatum interactions underlying impulsive choice and impulsive responding. Hum Brain Mapp 36:187–198.

Berry KJ, Mielke PW, Jr. (2000) A Monte Carlo investigation of the Fisher Z transformation for normal and nonnormal distributions. Psychol Rep 87:1101–1114.

Beucke JC, Sepulcre J, Talukdar T, Linnman C, Zschenderlein K, Endrass T, Kaufmann C, Kathmann N (2013) Abnormally high degree connectivity of the orbitofrontal cortex in obsessive-compulsive disorder. JAMA Psychiatry 70:619–629.

Bolla KI, Eldreth DA, London ED, Kiehl KA, Mouratidis M, Contoreggi C, Matochik JA, Kurian V, Cadet JL, Kimes AS, Funderburk FR, Ernst M (2003) Orbitofrontal cortex dysfunction in abstinent cocaine abusers performing a decision-making task. Neuroimage 19:1085–1094.

Bonson KR, Grant SJ, Contoreggi CS, Links JM, Metcalfe J, Weyl HL, Kurian V, Ernst M, London ED (2002) Neural systems and cue-induced cocaine craving. Neuropsychopharmacology 26:376–386.

Brewer JA, Potenza MN (2008) The neurobiology and genetics of impulse control disorders: relationships to drug addictions. Biochem Pharmacol 75:63–75.

Britt JP, Benaliouad F, McDevitt RA, Stuber GD, Wise RA, Bonci A (2012) Synaptic and behavioral profile of multiple glutamatergic inputs to the nucleus accumbens. Neuron 76:790–803.

Burke KA, Takahashi YK, Correll J, Brown PL, Schoenbaum G (2009) Orbitofrontal inactivation impairs reversal of Pavlovian learning by interfering with "disinhibition" of responding for previously unrewarded cues. Eur J Neurosci 30:1941–1946.

Burton AC, Nakamura K, Roesch MR (2015) From ventral-medial to dorsal-lateral striatum: neural correlates of reward-guided decision-making. Neurobiol Learn Mem 117:51–59.

Cachope R, Cheer JF (2014) Local control of striatal dopamine release. Front Behav Neurosci 8:188.

Canterberry M, Peltier MR, Brady KT, Hanlon CA (2016) Attenuated neural response to emotional cues in cocaine-dependence: a preliminary analysis of gender differences. Am J Drug Alcohol Abuse 42:577–586.

Cisler JM, Elton A, Kennedy AP, Young J, Smitherman S, Andrew James G, Kilts CD (2013) Altered functional connectivity of the insular cortex across prefrontal networks in cocaine addiction. Psychiatry Res 213:39–46.

Contreras-Rodriguez O, Martin-Perez C, Vilar-Lopez R, Verdejo-Garcia A (2017) Ventral and dorsal striatum networks in obesity: link to food craving and weight gain. Biol Psychiatry 81:789–796.

Dalley JW, Fryer TD, Brichard L, Robinson ES, Theobald DE, Laane K, Pena Y, Murphy ER, Shah Y, Probst K, Abakumova I, Aigbirhio FI, Richards HK, Hong Y, Baron JC, Everitt BJ, Robbins TW (2007) Nucleus accumbens D2/3 receptors predict trait impulsivity and cocaine reinforcement. Science 315:1267–1270.

Dalley JW, Robbins TW (2017) Fractionating impulsivity: neuropsychiatric implications. Nat Rev Neurosci 18:158–171.

Ding X, Lee SW (2013) Cocaine addiction related reproducible brain regions of abnormal default-mode network functional connectivity: a group ICA study with different model orders. Neurosci Lett 548:110–114.

Dong GH, Dong H, Wang M, Zhang J, Zhou W, Du X, Potenza MN (2021) Dorsal and ventral striatal functional connectivity shifts play a potential role in internet gaming disorder. Commun Biol 4:866.

Duvernoy HM (1999) The human brain. New York: Springer Verlag Wien.

Ersche KD, Meng C, Ziauddeen H, Stochl J, Williams GB, Bullmore ET, Robbins TW (2020) Brain networks underlying vulnerability and resilience to drug addiction. Proc Natl Acad Sci U S A 117:15253–15261.

Ersche KD, Lim TV, Murley AG, Rua C, Vaghi MM, White TL, Williams GB, Robbins TW (2021) Reduced glutamate turnover in the putamen is linked with automatic habits in human cocaine addiction. Biol Psychiatry 89:970–979.

Everitt BJ, Robbins TW (2005) Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. Nat Neurosci 8:1481–1489.

Everitt BJ, Robbins TW (2016) Drug addiction: updating actions to habits to compulsions ten years on. Annu Rev Psychol 67:23–50.

Fineberg NA, Potenza MN, Chamberlain SR, Berlin HA, Menzies L, Bechara A, Sahakian BJ, Robbins TW, Bullmore ET, Hollander E (2010) Probing compulsive and impulsive behaviors, from animal models to endophenotypes: a narrative review. Neuropsychopharmacology 35:591–604.

First M, Spitzer R, Williams J, Gibbon M (1995) Structured clinical interview for DSM-IV (SCID). Washington, DC: American Psychiatric Association.

Fotros A, Casey KF, Larcher K, Verhaeghe JA, Cox SM, Gravel P, Reader AJ, Dagher A, Benkelfat C, Leyton M (2013) Cocaine cue-induced dopamine release in amygdala and hippocampus: a high-resolution PET [(1)(8)F]fallypride study in cocaine dependent participants. Neuropsychopharmacology 38:1780–1788.

Fox MD, Raichle ME (2007) Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci 8:700–711.

Gawrysiak MJ, Jagannathan K, Regier P, Suh JJ, Kampman K, Vickery T, Childress AR (2017) Unseen scars: cocaine patients with prior trauma evidence heightened resting state functional connectivity (RSFC) between the amygdala and limbic-striatal regions. Drug Alcohol Depend 180:363–370.

Goldstein RZ, Volkow ND (2011) Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. Nat Rev Neurosci 12:652–669.

Goldstein RZ, Volkow ND, Wang GJ, Fowler JS, Rajaram S (2001) Addiction changes orbitofrontal gyrus function: involvement in response inhibition. Neuroreport 12:2595–2599.

Goto Y, Grace AA (2005) Dopamine-dependent interactions between limbic and prefrontal cortical plasticity in the nucleus accumbens: disruption by cocaine sensitization. Neuron 47:255–266.

Gu H, Salmeron BJ, Ross TJ, Geng X, Zhan W, Stein EA, Yang Y (2010) Mesocorticolimbic circuits are impaired in chronic cocaine users as demonstrated by resting-state functional connectivity. Neuroimage 53:593–601.

Hu YZ, Salmeron BJ, Gu H, Stein EA, Yang YH (2015) Impaired functional connectivity within and between frontostriatal circuits and its association with compulsive drug use and trait impulsivity in cocaine addiction. JAMA Psychiatry 72:584–592.

Ide JS, Li HT, Chen Y, Le TM, Li CSP, Zhornitsky S, Li CR (2020) Gray matter volumetric correlates of behavioral activation and inhibition system traits in children: an exploratory voxel-based morphometry study of the ABCD project data. Neuroimage 220:117085.

Ito R, Dalley JW, Robbins TW, Everitt BJ (2002) Dopamine release in the dorsal striatum during cocaine-seeking behavior under the control of a drug-associated cue. J Neurosci 22:6247–6253.

Jenkins GM, Watts DG (1968) Spectral analysis and its applications. San Francisco, CA: Holden-Day.

Kelly C, Zuo XN, Gotimer K, Cox CL, Lynch L, Brock D, Imperati D, Garavan H, Rotrosen J, Castellanos FX, Milham MP (2011)

Reduced interhemispheric resting state functional connectivity in cocaine addiction. Biol Psychiatry 69:684–692.
Knackstedt LA, Trantham-Davidson HL, Schwendt M (2014) The role of ventral and dorsal striatum mGluR5 in relapse to cocaine-seeking and extinction learning. Addict Biol 19:87–101.
Konova AB, Moeller SJ, Tomasi D, Volkow ND, Goldstein RZ (2013) Effects of methylphenidate on resting-state functional connectivity of the mesocorticolimbic dopamine pathways in cocaine addiction. JAMA Psychiatry 70:857–868.
Li CS, Ide JS, Zhang S, Hu S, Chao HH, Zaborszky L (2014) Resting state functional connectivity of the basal nucleus of Meynert in humans: in comparison to the ventral striatum and the effects of age. Neuroimage 97:321–332.
Lim TV, Cardinal RN, Bullmore ET, Robbins TW, Ersche KD (2021) Impaired learning from negative feedback in stimulant use disorder: dopaminergic modulation. Int J Neuropsychopharmacol 24:867–878.
Lucantonio F, Stalnaker TA, Shaham Y, Niv Y, Schoenbaum G (2012) The impact of orbitofrontal dysfunction on cocaine addiction. Nat Neurosci 15:358–366.
Luscher C, Robbins TW, Everitt BJ (2020) The transition to compulsion in addiction. Nature Reviews Neuroscience 21:247–263.
Macmillan NA, Creelman CD (2005) Detection theory: a user's guide (2nd ed.). New York: Psychological Press.
Martinez D, Narendran R, Foltin RW, Slifstein M, Hwang DR, Broft A, Huang Y, Cooper TB, Fischman MW, Kleber HD, Laruelle M (2007) Amphetamine-induced dopamine release: markedly blunted in cocaine dependence and predictive of the choice to self-administer cocaine. Am J Psychiatry 164:622–629.
McClure SM, Laibson DI, Loewenstein G, Cohen JD (2004) Separate neural systems value immediate and delayed monetary rewards. Science 306:503–507.
Minogianis EA, Servonnet A, Filion MP, Samaha AN (2019) Role of the orbitofrontal cortex and the dorsal striatum in incentive motivation for cocaine. Behav Brain Res 372:112026.
Morein-Zamir S, Simon Jones P, Bullmore ET, Robbins TW, Ersche KD (2015) Take it or leave it: prefrontal control in recreational cocaine users. Transl Psychiatry 5:e582.
Moreno-Lopez L, Catena A, Fernandez-Serrano MJ, Delgado-Rico E, Stamatakis EA, Perez-Garcia M, Verdejo-Garcia A (2012) Trait impulsivity and prefrontal gray matter reductions in cocaine dependent individuals. Drug Alcohol Depend 125:208–214.
Moreno-Lopez L, Albein-Urios N, Martinez-Gonzalez JM, Soriano-Mas C, Verdejo-Garcia A (2017) Neural correlates of impaired self-awareness of apathy, disinhibition and dysexecutive deficits in cocaine-dependent individuals. Addict Biol 22:1438–1448.
Mukherjee J, Yang ZY, Brown T, Lew R, Wernick M, Ouyang XH, Yasillo N, Chen CT, Mintzer R, Cooper M (1999) Preliminary assessment of extrastriatal dopamine D-2 receptor binding in the rodent and nonhuman primate brains using the high affinity radioligand, F-18-fallypride. Nucl Med Biol 26:519–527.
Muller CP, Carey RJ, De Souza Silva MA, Jocham G, Huston JP (2002) Cocaine increases serotonergic activity in the hippocampus and nucleus accumbens in vivo: 5-HT1a-receptor antagonism blocks behavioral but potentiates serotonergic activation. Synapse 45:67–77.
Murray JE, Dilleen R, Pelloux Y, Economidou D, Dalley JW, Belin D, Everitt BJ (2014) Increased impulsivity retards the transition to dorsolateral striatal dopamine control of cocaine seeking. Biol Psychiatry 76:15–22.
Oh H, Lee J, Gosnell SN, Patriquin M, Kosten T, Salas R (2020) Orbitofrontal, dorsal striatum, and habenula functional connectivity in psychiatric patients with substance use problems. Addict Behav 108:106457.
Pascoli V, Terrier J, Espallergues J, Valjent E, O'Connor EC, Luscher C (2014) Contrasting forms of cocaine-evoked plasticity control components of relapse. Nature 509:459–464.
Pascoli V, Terrier J, Hiver A, Luscher C (2015) Sufficiency of mesolimbic dopamine neuron stimulation for the progression to addiction. Neuron 88:1054–1066.
Pascoli V, Hiver A, Van Zessen R, Loureiro M, Achargui R, Harada M, Flakowski J, Luscher C (2018) Stochastic synaptic plasticity underlying compulsion in a model of addiction. Nature 564:366–371.
Patton JH, Stanford MS, Barratt ES (1995) Factor structure of the Barratt impulsiveness scale. J Clin Psychol 51:768–774.
Porrino LJ, Lyons D, Smith HR, Daunais JB, Nader MA (2004) Cocaine self-administration produces a progressive involvement of limbic, association, and sensorimotor striatal domains. J Neurosci 24:3554–3562.
Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE (2012) Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. Neuroimage 59:2142–2154.
Risinger RC, Salmeron BJ, Ross TJ, Amen SL, Sanfilipo M, Hoffmann RG, Bloom AS, Garavan H, Stein EA (2005) Neural correlates of high and craving during cocaine self-administration using BOLD fMRI. Neuroimage 26:1097–1108.
Robbins TW (2007) Shifting and stopping: fronto-striatal substrates, neurochemical modulation and clinical implications. Philos Trans R Soc Lond, B, Biol Sci 362:917–932.
Rolls ET (2000) The orbitofrontal cortex and reward. Cereb Cortex 10:284–294.
Rolls ET, Baylis LL (1994) Gustatory, olfactory, and visual convergence within the primate orbitofrontal cortex. J Neurosci 14:5437–5452.
Schoenbaum G, Roesch MR, Stalnaker TA (2006) Orbitofrontal cortex, decision-making and drug addiction. Trends Neurosci 29:116–124.
Sinha R, Lacadie C, Skudlarski P, Fulbright RK, Rounsaville BJ, Kosten TR, Wexler BE (2005) Neural activity associated with stress-induced cocaine craving: a functional magnetic resonance imaging study. Psychopharmacology 183: 171–180.
Smith KS, Graybiel AM (2013) A dual operator view of habitual behavior reflecting cortical and striatal dynamics (vol 79, pg 1, 2013). Neuron 79:608.
Smyser CD, Inder TE, Shimony JS, Hill JE, Degnan AJ, Snyder AZ, Neil JJ (2010) Longitudinal analysis of neural network development in preterm infants. Cereb Cortex 20:2852–2862.
Stewart JL, Connolly CG, May AC, Tapert SF, Wittmann M, Paulus MP (2014) Cocaine dependent individuals with attenuated striatal activation during reinforcement learning are more susceptible to relapse. Psychiatry Res 223:129–139.
Sussner BD, Smelson DA, Rodrigues S, Kline A, Losonczy M, Ziedonis D (2006) The validity and reliability of a brief measure of cocaine craving. Drug Alcohol Depend 83:233–237.
Sutherland MT, McHugh MJ, Pariyadath V, Stein EA (2012) Resting state functional connectivity in addiction: lessons learned and a road ahead. Neuroimage 62:2281–2295.
Tiffany ST (1990) A cognitive model of drug urges and drug-use behavior: role of automatic and nonautomatic processes. Psychol Rev 97:147–168.

Tiffany ST, Singleton E, Haertzen CA, Henningfield JE (1993) The development of a cocaine craving questionnaire. Drug Alcohol Depend 34:19–28.

Tomasi D, Volkow ND (2014) Functional connectivity of substantia nigra and ventral tegmental area: maturation during adolescence and effects of ADHD. Cereb Cortex 24:935–944.

Tomasi D, Wang GJ, Wang R, Caparelli EC, Logan J, Volkow ND (2015) Overlapping patterns of brain activation to food and cocaine cues in cocaine abusers: association to striatal D2/D3 receptors. Hum Brain Mapp 36:120–136.

Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M (2002) Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 15:273–289.

Van Dijk KR, Sabuncu MR, Buckner RL (2012) The influence of head motion on intrinsic functional connectivity MRI. Neuroimage 59:431–438.

Vanderschuren LJ, Di Ciano P, Everitt BJ (2005) Involvement of the dorsal striatum in cue-controlled cocaine seeking. J Neurosci 25:8665–8670.

Vaquero L, Camara E, Sampedro F, Perez de Los Cobos J, Batlle F, Fabregas JM, Sales JA, Cervantes M, Ferrer X, Lazcano G, Rodriguez-Fornells A, Riba J (2017) Cocaine addiction is associated with abnormal prefrontal function, increased striatal connectivity and sensitivity to monetary incentives, and decreased connectivity outside the human reward circuit. Addict Biol 22:844–856.

Volkow ND, Baler RD (2015) NOW vs LATER brain circuits: implications for obesity and addiction. Trends in Neurosciences 38:345–352.

Volkow ND, Morales M (2015) The brain on drugs: from reward to addiction. Cell 162:712–725.

Volkow ND, Wang GJ, Fowler JS, Tomasi D, Telang F (2011) Addiction: beyond dopamine reward circuitry. Proc Natl Acad Sci U S A 108:15037–15042.

Volkow ND, Wang GJ, Telang F, Fowler JS, Logan J, Childress AR, Jayne M, Ma Y, Wong C (2006) Cocaine cues and dopamine in dorsal striatum: mechanism of craving in cocaine addiction. J Neurosci 26:6583–6588.

Walter M, Denier N, Gerber H, Schmid O, Lanz C, Brenneisen R, Riecher-Rossler A, Wiesbeck GA, Scheffler K, Seifritz E, McGuire P, Fusar-Poli P, Borgwardt S (2015) Orbitofrontal response to drug-related stimuli after heroin administration. Addict Biol 20:570–579.

Wang W, Zhornitsky S, Zhang S, Li CR (2021) Noradrenergic correlates of chronic cocaine craving: neuromelanin and functional brain imaging. Neuropsychopharmacology 46:851–859.

White NM (1989) Reward or reinforcement: what's the difference? Neurosci Biobehav Rev 13:181–186.

Wilcox CE, Teshiba TM, Merideth F, Ling J, Mayer AR (2011) Enhanced cue reactivity and fronto-striatal functional connectivity in cocaine use disorders. Drug Alcohol Depend 115:137–144.

Wong DF et al. (2006) Increased occupancy of dopamine receptors in human striatum during cue-elicited cocaine craving. Neuropsychopharmacology 31:2716–2727.

Zhang JT, Yao YW, Li CS, Zang YF, Shen ZJ, Liu L, Wang LJ, Liu B, Fang XY (2016) Altered resting-state functional connectivity of the insula in young adults with Internet gaming disorder. Addict Biol 21:743–751.

Zhang S, Li CR (2018) Ventral striatal dysfunction in cocaine dependence - difference mapping for subregional resting state functional connectivity. Transl Psychiatry 8:119.

Zhang S, Hu S, Fucito LM, Luo X, Mazure CM, Zaborszky L, Li CR (2017) Resting-state functional connectivity of the basal nucleus of meynert in cigarette smokers: dependence level and gender differences. Nicotine Tob Res 19:452–459.

Zhou F, Zimmermann K, Xin F, Scheele D, Dau W, Banger M, Weber B, Hurlemann R, Kendrick KM, Becker B (2018) Shifted balance of dorsal versus ventral striatal communication with frontal reward and regulatory regions in cannabis-dependent males. Hum Brain Mapp 39:5062–5073.

Zhang S, Zhornitsky S, Angarita GA, Li CR (2020) Hypothalamic response to cocaine cues and cocaine addiction severity. Addict Biol 25:e12682.

Zhukovsky P, Morein-Zamir S, Ziauddeen H, Fernandez-Egea E, Meng C, Regenthal R, Sahakian BJ, Bullmore ET, Robbins TW, Dalley JW, Ersche KD (2021) Prefrontal cortex activation and stopping performance underlie the beneficial effects of atomoxetine on response inhibition in healthy and cocaine use disorder volunteers. Biol Psychiatry Cogn Neurosci Neuroimaging. 2021 Sep 8;S2451-9022(21)00252-4. doi: 10.1016/j.bpsc.2021.08.010. Online ahead of print.

Zimmermann K, Yao S, Heinz M, Zhou F, Dau W, Banger M, Weber B, Hurlemann R, Becker B (2018) Altered orbitofrontal activity and dorsal striatal connectivity during emotion processing in dependent marijuana users after 28 days of abstinence. Psychopharmacology 235:849–859.

Zou KH, O'Malley AJ, Mauri L (2007) Receiver-operating characteristic analysis for evaluating diagnostic tests and predictive models. Circulation 115:654–657.