

REGULAR RESEARCH ARTICLE

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

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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

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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 progression 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

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: $DVARs(t) = \sqrt{\langle |I(t) - I(t-1)|^2 \rangle}$, 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.

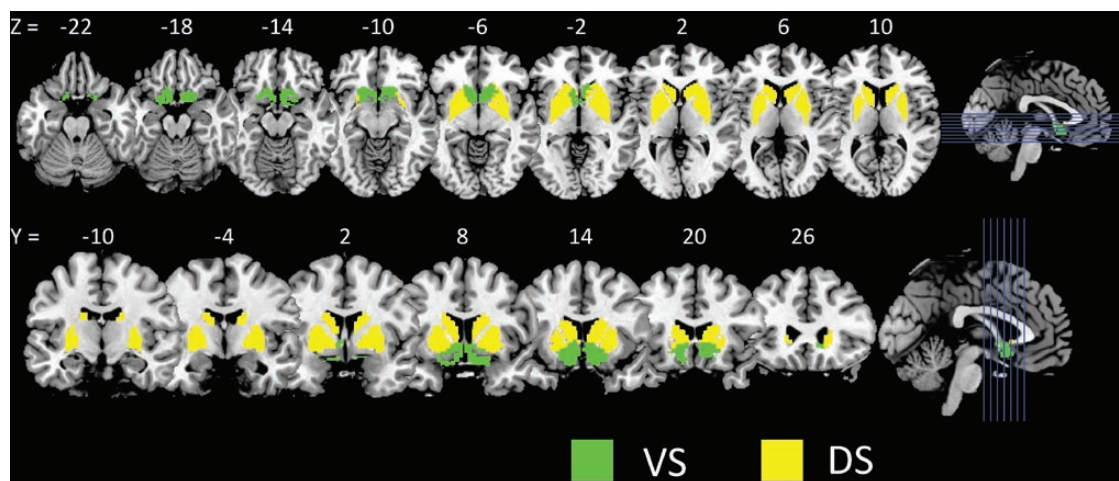


Figure 1. Seed regions: ventral (VS, green) and dorsal (DS, yellow) striatum are shown on axial ($z = -22$ to $+10$) and coronal ($y = -10$ to $+26$) sections of the brain.

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 $\pm$ 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 $P = .05/(4 \times 3) = .0042$. 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 P s $> .20$). 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 P s $> .065$). No DS rsFC was correlated with BIS total or subscores (all P s $> .35$).

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)			Side	Identified brain region
		x	y	z		
mm ³	Z					
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.

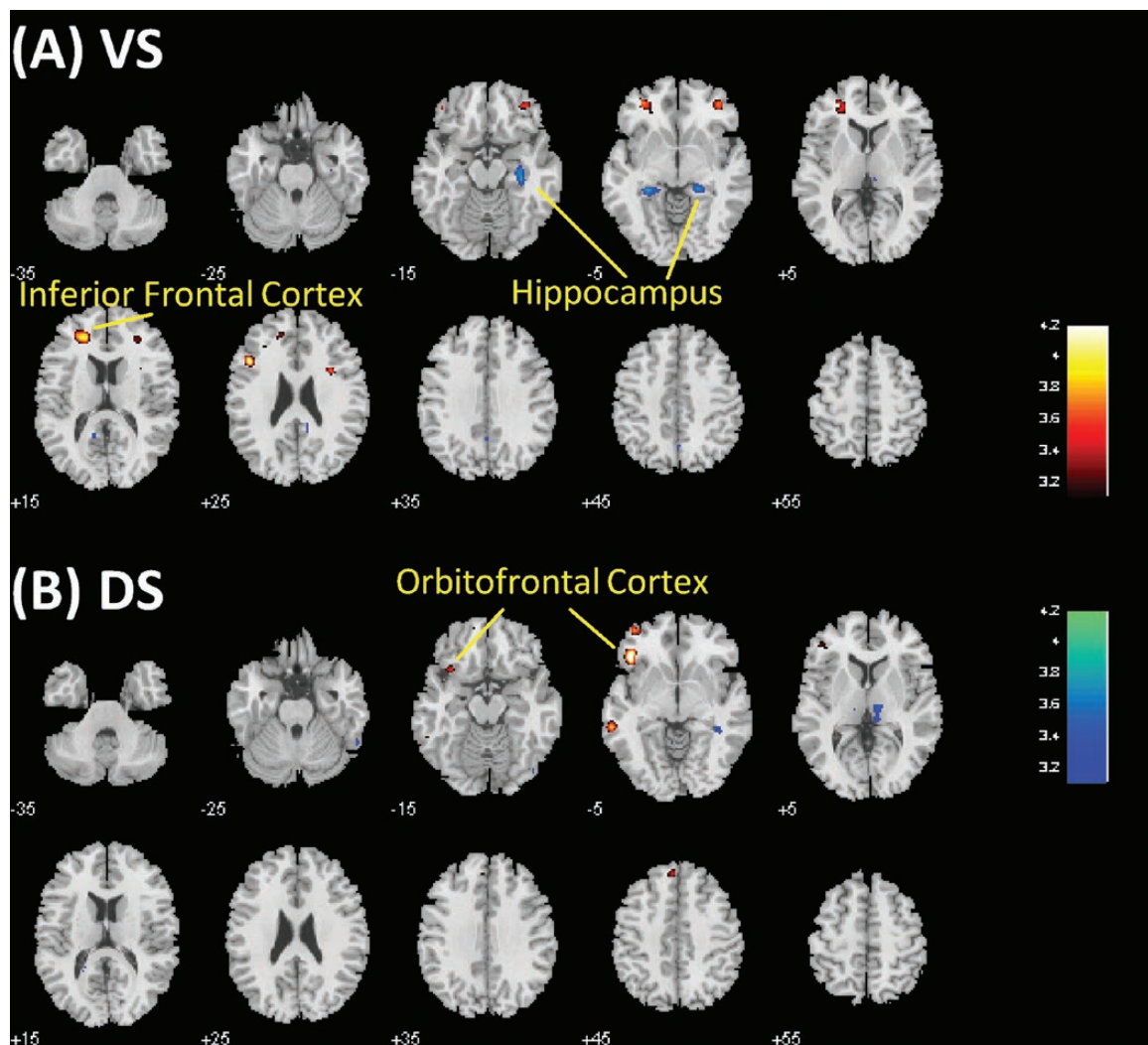


Figure 2. Brain regions showing differences between CDs (n=122) and HCs (n=122) in ventral (VS) and dorsal (DS) striatal rsFC, evaluated at voxel $P < .001$ uncorrected and cluster $P < .05$ family-wise error-corrected. Warm and cool voxels each show higher and lower rsFC with the seed region in CDs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

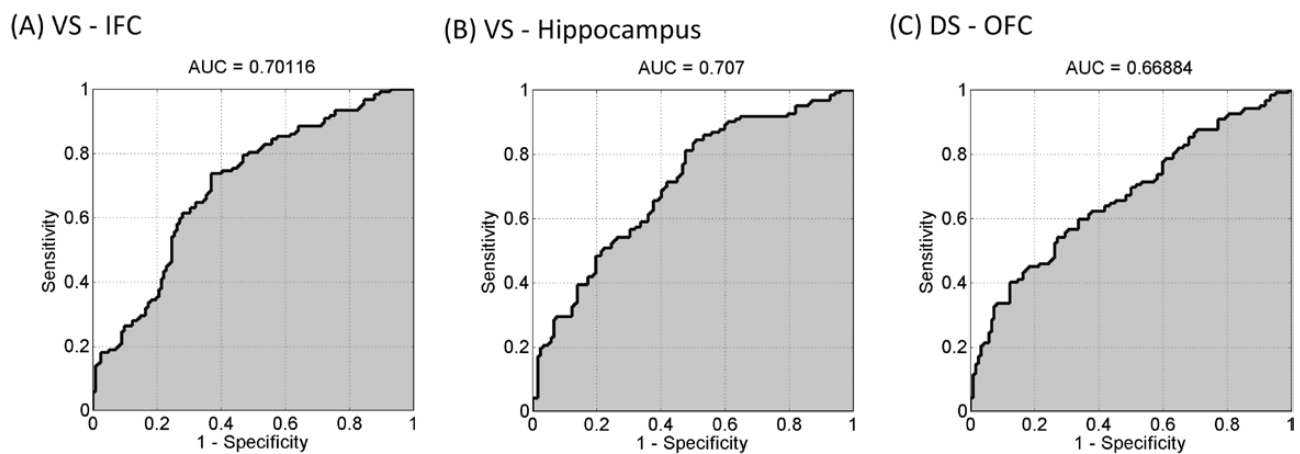


Figure 3. Receiver operating characteristic analysis showed that the VS rsFC with the left IFC (area under the curve or AUC=0.70) and with the hippocampus (AUC=0.71) were slightly more accurate than DS rsFC with the left OFC (AUC=0.67) in distinguishing CDs and HCs. DS, dorsal striatum; IFC, inferior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

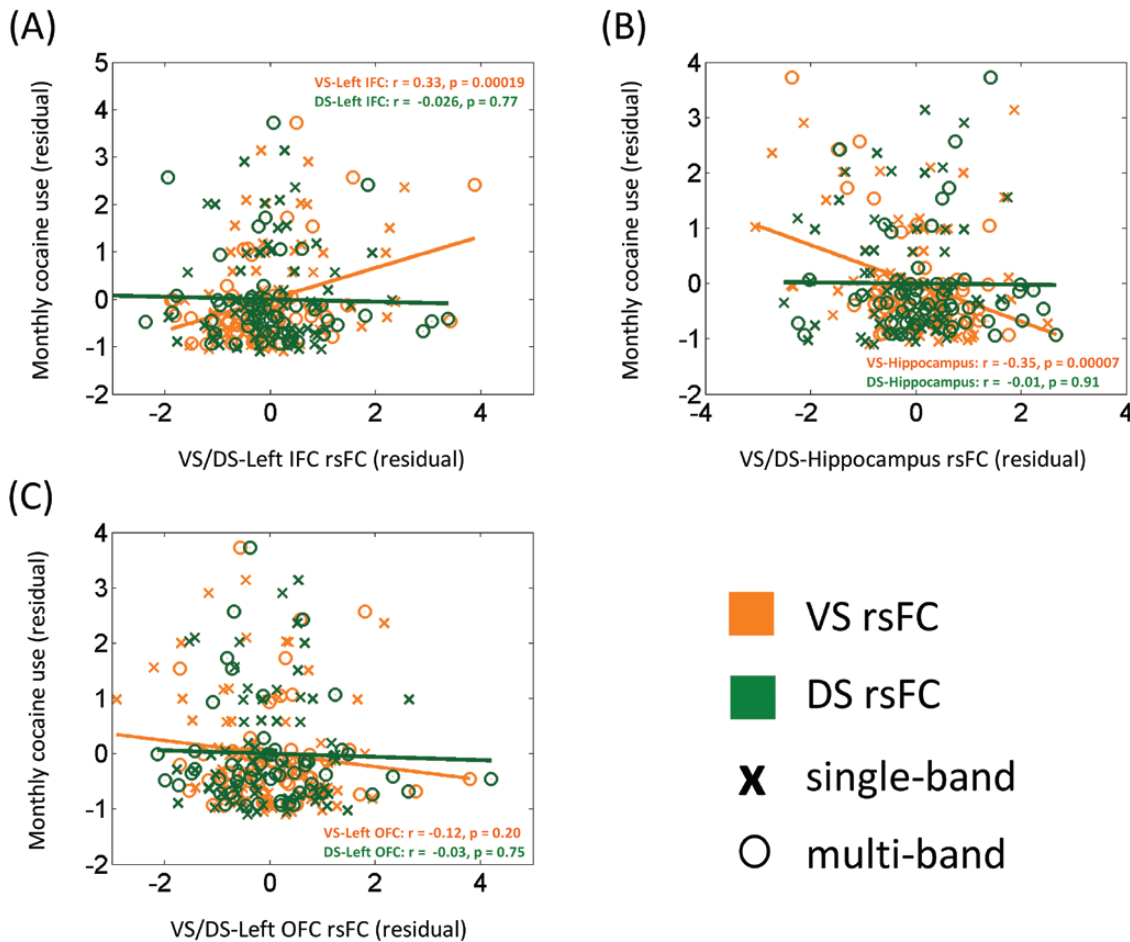


Figure 4. Linear regressions of VS/DS rsFC (z scores) of regions of interest vs average total monthly amount of cocaine use in the prior year, with age, sex, and years of drinking as covariates, in CDs. (A) VS/DS-left IFC. (B) VS/DS-hippocampus. (C) VS/DS-left OFC. Each data point represents the residual 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;

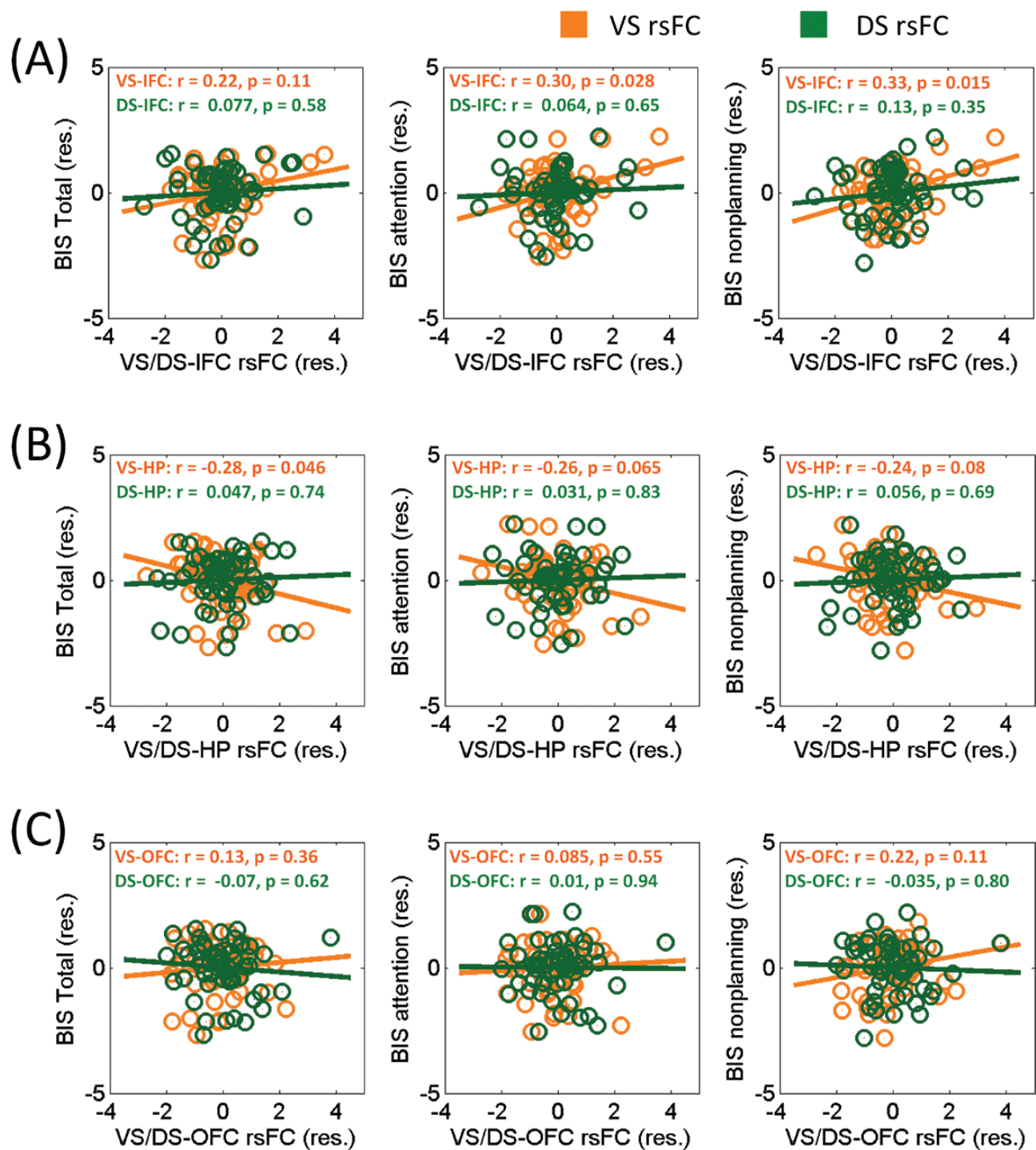


Figure 5. Linear regressions of VS/DS rsFC (z scores) of regions of interest vs BIS-11 total score, attention sub-score, and non-planning sub-score, with age, sex, and years of drinking as covariates, in CDs. (A) VS/DS-left IFC. (B) VS/DS-hippocampus. (C) VS/DS-left OFC. Each data point represents the 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

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