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Neural Correlates of Substance Abuse: Reduced Functional Connectivity Between Areas Underlying Reward and Cognitive Control

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Abstract: Substance use disorders (SUD) have been associated with dysfunction in reward processing, habit formation, and cognitive-behavioral control. Accordingly, neurocircuitry models of addiction highlight roles for nucleus accumbens, dorsal striatum, and prefrontal/anterior cingulate cortex. However, the precise nature of the disrupted interactions between these brain regions in SUD, and the psychological correlates thereof, remain unclear. Here we used magnetic resonance imaging to measure rest-state functional connectivity of three key striatal nuclei (nucleus accumbens, dorsal caudate, and dorsal putamen) in a sample of 40 adult male prison inmates (n = 22 diagnosed with SUD; n = 18 without SUD). Relative to the non-SUD group, the SUD group exhibited significantly lower functional connectivity between the nucleus accumbens and a network of frontal cortical regions involved in cognitive control (dorsal anterior cingulate cortex, dorsolateral prefrontal cortex, and frontal operculum). There were no group differences in functional connectivity for the dorsal caudate or dorsal putamen. Moreover, the SUD group exhibited impairments in laboratory measures of cognitive-behavioral control, and individual differences in functional connectivity between nucleus accumbens and the frontal cortical regions were related to individual differences in measures of cognitive-behavioral control across groups. The strength of the relationship between functional connectivity and cognitive control did not differ between groups. These results indicate that SUD is associated with abnormal interactions between subcortical areas that process reward (nucleus accumbens) and cortical areas that govern cognitive-behavioral control. *Hum Brain Mapp 35:4282–4292, 2014.* © 2014 Wiley Periodicals, Inc.

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INTRODUCTION

Substance Use Disorder (SUD) involves a chronic, recurrent pattern of drug or alcohol use that negatively impacts physical and psychological well-being, occupational and family obligations, and social relationships [APA, 1994]. Across substances of abuse, a similar pattern of SUD etiopathology is apparent, progressing from an initial stage in which occasional use elicits a rewarding hedonic effect, to a pathological stage characterized by escalated use, loss of control over intake, and the emergence of compulsive drug seeking behaviors [Everitt and Robbins, 2005; Koob and Volkow, 2010]. This framework highlights the ventral striatum/nucleus accumbens (NAc) and dorsal striatum (caudate and putamen) as key subcortical nuclei involved in the progression from the initial reinforcing effects of drug use to habitual, compulsive drug seeking and drug taking [Everitt and Robbins, 2005]. Dysfunction in neocortex, particularly in frontal lobe structures implicated in cognitive-behavioral control (e.g., dorsal anterior cingulate cortex and dorsolateral prefrontal cortex), has been linked to loss of control over drug intake, a critical step in the progression of SUD pathology [George and Koob, 2010]. Accordingly, previous neuroimaging studies of SUD have revealed structural and functional changes throughout the striatum, as well as in cortical regions implicated in cognitive-behavioral control [Baler and Volkow, 2006; Hester and Garavan, 2004; Jentsch and Taylor, 1999; Kaufman et al., 2003; Volkow et al., 2003, 2006; Vollstadt-Klein et al., 2010].

In addition to modular dysfunction within discrete brain regions, neurobiological models of SUD posit that impaired communication between brain regions may contribute significantly to behavioral deficits characteristic of SUD [Koob and Volkow, 2010; Sutherland et al., 2012]. Thus, neuropsychological studies relating circuit-level interactions between brain regions to particular dimensions of behavioral dysfunction are critical for testing the leading psychobiological models of SUD. Rest-state functional connectivity (rsFC) magnetic resonance imaging, which permits in vivo measurement of the degree of correlated activity (i.e., the strength of interaction) between macroscopic brain regions, offers a unique opportunity to examine interactions between brain regions implicated in SUD [Biswal et al., 1995; Fox and Raichle, 2007].

A number of previous studies have examined rsFC in substance-using populations, albeit with mixed results. Among the studies that have explicitly tested connectivity with the striatum, some have observed increased fronto-striatal connectivity [Ma et al., 2010; Wilcox et al., 2011], whereas others have identified decreased fronto-striatal connectivity [Upadhyay et al., 2010]. Additionally, several studies have failed to identify any association between substance use and striatal connectivity [Gu et al., 2010; see Sutherland et al., 2012 for a review]. The failure to replicate connectivity findings across studies may result from several factors, including divergence of substances of abuse (e.g., cocaine vs. opiates), the choice of seed regions in connectivity (cortical seeds vs. striatal seeds), the concurrent use of drugs of abuse (actively using vs. prolonged abstinence), or the suitability of the "control" group used for between-group comparisons. Further, among the published rsFC studies, none have specifically examined connectivity for both dorsal and ventral striatum, and none have related the functional connectivity within specific fronto-striatal circuits to particular domains of psychological function.

In this study, we used rsFC to investigate differences in striatal connectivity between a population of prison inmates with SUD and a matched sample of prisoners without SUD. We hypothesized that inmates with SUD would exhibit deficient rsFC between striatal nuclei and cortical regions involved in cognitive-behavioral control. Moreover, we administered behavioral-task and self-report measures to test the hypothesis that functional connectivity between the striatum and identified cortical regions would be related to individual differences in cognitive control abilities.

METHODS

Participants

Participants were adult male inmates recruited from a medium-security Wisconsin correctional institution. Inmates were eligible if they met the following criteria: 45 years of age or younger, IQ greater than 70, no history of psychosis or bipolar disorder, no history of significant head injury or post-concussion symptoms, and not currently taking psychotropic medications. Diagnosis of SUD was determined with the Structured Clinical Interview for DSM-IV Disorders (SCID) [First, 2002]. Participants were classified as SUD if they met criteria for abuse or dependence on any of the following substances: alcohol, cannabis, cocaine, opioids, stimulants, sedatives, or hallucinogens. In addition, inmates were assessed for psychopathy prior to participation, as they were originally recruited for a study on the neural correlates of psychopathy [Ly et al., 2012; Motzkin et al., 2011]. Of the 41 participants who underwent MRI data collection, 1 was excluded for excessive motion. Of the remaining 40 participants, 22 met criteria for SUD (SUD group) and 18 did not (non-SUD group).

SUD and non-SUD inmates did not significantly differ with respect to age, general intellectual ability (IQ or backward digit span), or overall psychopathy severity (Table I). The vast majority of individuals in the SUD group (18/22) met abuse/dependence criteria for multiple substances, with an average of 3.2 ± 1.5 abused substances per subject. Only 4 of the 22 SUD participants met criteria for SUD on a single substance (3 alcohol, 1 cocaine), 3/22 abused 2 substances (alcohol or cocaine with cannabis), and 15/22 abused 3 or more substances. For each of the other five substances assessed (sedatives, cannabis, stimulants, opiates, and hallucinogens), abuse always cooccurred with abuse of at least one other substance. Although the most recent version of the DSM (DSM-5) abolished separate abuse/dependence criteria in favor of a single substance use diagnosis with graded manifestations [APA, 2013], the preponderance of subjects meeting DSM-IV "dependence" criteria (17/22) highlights the severity of substance abuse problems in our sample. In addition to the SCID, we collected self-report data relevant to SUD with two other instruments, the Externalizing Spectrum Inventory-Substance Abuse subscale (ESI-SUB) and Michigan Assessment Screening Test for Alcohol and Drugs (MAST-AD). Problem drug use was assessed with the SUB subscale of the 100-item version of the ESI [Hall et al., 2007; Krueger et al., 2007], which has been validated in criminal offender populations [Venables and Patrick, 2012]. ESI-SUB items include marijuana use, marijuana problems, drug use, drug problems, alcohol use, and alcohol problems. The MAST-AD is a modification of the 24-item Michigan Alcohol Screening Test in which questions have been broadened to reference drug use, and has been shown to be a sensitive indicator of both alcohol and drug related problems [Reid et al., 1999; Selzer, 1971; Westermeyer et al., 2004]. A subset of $n = 19$ SUD and $n = 12$ non-SUD participants completed both scales. Groups were significantly different on both measures (Table I).

TABLE I. Participant group characteristics

Variable	SUD ($n = 22$)	non-SUD ($n = 18$)	P
Demographic			
Age	32.0 (7.0)	31.7 (7.5)	0.90
Race (Cauc:AA:Oth)	21:0:1	12:6:0	0.03
Neuropsychological			
IQ[a]	98.7 (11.6)	102.7 (10.8)	0.29
Digit Span Backward	6.7 (2.4)	7.0 (3.5)	0.96
Anxiety/Neg Affect[b]	11.9 (8.4)	12.7 (9.7)	0.77
Psychopathy[c]			
PCL-R total	24.4 (9.5)	21.4 (9.2)	0.33
Factor 1	8.1 (4.4)	8.3 (3.8)	0.88
Factor 2	13.9 (4.8)	11.0 (5.5)	0.08
P:NonP	13:9	7:11	0.34
SUD[d]			
Alcohol[d]			
Prevalence	20/22	0/18	<0.0001
Age of onset	20.6 (5.2)	n/a	
Cannabis[d]			
Prevalence	18/22	0/18	<0.0001
Age of onset	18.7 (5.9)	n/a	
Cocaine[d]			
Prevalence	9/22	0/18	0.001
Age of onset	20.0 (4.5)	n/a	
Stimulants[d]			
Prevalence	6/22	0/18	0.02
Age of onset	20.3 (5.5)	n/a	
Opioids[d]			
Prevalence	9/22	0/18	0.001
Age of onset	21.3 (6.3)	n/a	
Sedatives[d]			
Prevalence	3/22	0/18	0.23
Age of onset	23.0 (3.6)	n/a	
Hallucinogens[d]			
Prevalence	5/22	0/18	0.05
Age of onset	18.6 (2.5)	n/a	
ESI-SUB[e]	16.0 (3.0)	9.3 (3.6)	<0.0001
MAST-AD[f]	12.0 (3.7)	5.5 (3.3)	<0.0001

[a]Based on Shipley Institute of Living Scale (Zachary, 1986).
[b]Based on Welsh Anxiety Scale.
[c]Based on Psychopathy Checklist-Revised (Hare, 2003).
[d]Based on diagnosis of abuse or dependence in the SCID.
[e]ESI–SUB subscale.
[f]Michigan Assessment Screening Test for Alcohol and Drugs. *P*-values for race distribution, psychopath to nonpsychopath ratio (P:NonP) and SUD prevalence were computed with Fisher's Exact Test. All other *P*-values are based on t-tests (means presented followed by standard deviations in parentheses).

MRI DATA COLLECTION

All MRI data were acquired using the Mind Research Network's Siemens 1.5 T Avanto Mobile MRI System on correctional facility grounds. Rest-state functional images were collected while subjects passively viewed a fixation cross (T2*-weighted gradient-echo echoplanar functional images: TR = 2000 ms, TE = 39 ms, flip angle = 75°, FOV = 24 × 24 cm, matrix = 64 × 64, slice thickness = 4 mm, gap = 1 mm, voxel size = 3.75 × 3.75 × 5 mm, 27 sequential axial oblique slices). Rest-state scans lasted 5.5 min (158 volumes). A high-resolution T1-weighted structural image was acquired using a four-echo MPRAGE sequence (TR = 2530; TE = 1.64, 3.5, 5.36, 7.22 ms; flip angle = 7°, FOV = 256 × 256 mm, matrix = 128 × 128, slice thickness = 1.33 mm, no gap, voxel size = 1 × 1 × 1.33 mm, 128 interleaved sagittal slices). All four echos were averaged into a single high-resolution image for subsequent analysis.

MRI DATA PROCESSING

Preprocessing

All fMRI data analysis was performed using AFNI [Cox, 1996] and FSL software. Individual EPI data were slice time corrected, motion corrected, despiked, bandpass filtered ($0.009 < f < 0.08$), and spatially smoothed with a four-millimeter full width at half maximum Gaussian

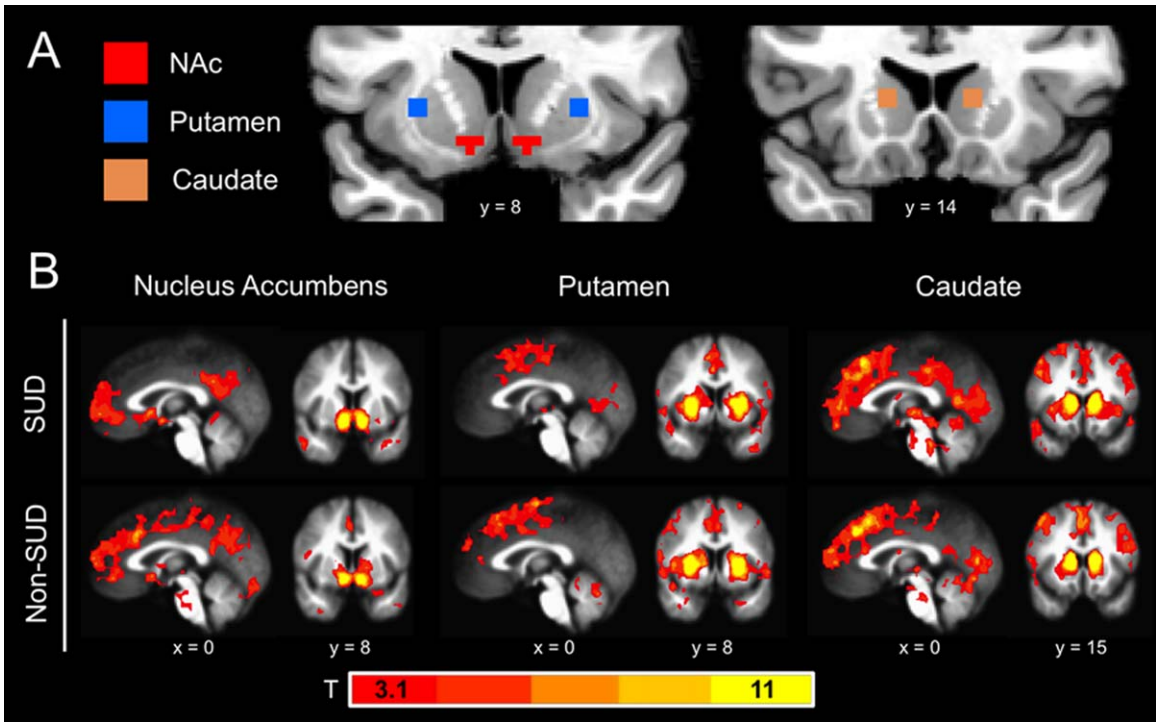

Figure 1.

Striatal functional connectivity. **A**: Location of the three striatal seeds in two coronal sections (with Talairach *y* coordinates). Each seed included regions in both hemispheres. NAc (±9, +8, −7); Putamen (±25, +8, +5); Caudate (±13, +15, +8). **B**: Within-groups functional connectivity maps for each seed region are presented at a $P_{FWE} < 0.05$. Colors indicate the magnitude of the T-statistic, set to a peak value of 11 for display purposes. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

kernel [Fox et al., 2005; Sacchet and Knutson, 2012]. Any subject with motion greater than two millimeters between adjacent volumes was excluded from further analysis (one SUD participant). There was no significant difference between groups in root mean squared head position change ($P = 0.42$). EPI time series data and high-resolution T1 images were normalized to the Talairach coordinate system [Talairach and Tournoux, 1988] using a 12-parameter linear warp. EPI data were resampled to three-millimeter cubic voxels for subsequent functional connectivity analyses.

Region of Interest (ROI) Selection and Correlation Analysis

To calculate the functional connectivity of key striatal nuclei implicated in SUD, we seeded three bilateral ROIs (Fig. 1A): NAc, caudate, and putamen. Seed coordinates correspond respectively to the inferior ventral striatum (VSi), dorsal caudate (DC), and dorsal rostral putamen (DRP) ROIs reported in a previous rsFC study [Di Martino et al., 2008], which was based on a large-scale meta-analysis of striatal connectivity [Postuma and Dagher, 2006]. The selected seeds have been shown to exhibit distinct, but overlapping, patterns of connectivity at rest, which correspond to known anatomical connections between striatum and cortex [Di Martino et al., 2008; Selemon and Goldman-Rakic, 1985].

Functional connectivity was assessed by computing whole brain correlations with the mean time series derived separately from each of the three seed ROIs. The mean time series was included in a GLM with eight regressors of no interest, including six motion parameters from motion correction (three translations, three rotations), the ventricular time series, the white matter time series, and a second order polynomial to model baseline signal and slow drift [Fox et al., 2005]. Voxelwise correlation coefficients for each ROI were converted to z-scores via Fisher's r-to-z transform and the resulting z-score maps were entered into second level statistical analyses.

Statistical Analyses of Correlation Maps

To compare striatal functional connectivity between SUD and non-SUD inmates, we performed voxelwise two-sample t-tests on the z-score maps derived from each seed

ROI. Group difference maps were family wise error (FWE) corrected for multiple comparisons across the whole brain at the cluster level ($P_{corrected} < 0.05$), using a height threshold of $P < 0.005$ [Carp, 2012; Forman et al., 1995]. Cluster extents were calculated with 3dClustSim and 3dFWHMx in AFNI, using the estimated smoothness of voxelwise residual maps from the whole-brain connectivity analysis and the number of voxels in the brain mask. A Bonferroni-corrected alpha of 0.0166 was used to account for multiple comparisons at the group level, based on the three striatal ROIs ($\alpha = 0.05/3 = 0.0166$). In our data, a corrected $P_{FWE} < 0.0166$ was achieved using a minimum cluster extent threshold of 49 voxels (1323 mm^3).

Assessment of Cognitive-Behavioral Control

To measure participants' capacity for cognitive-behavioral control, we administered two psychological assessments: one performance-based test and one self-report scale. Cognitive control performance was measured with the Color-Word Interference Test (CWIT), a subtest of the Delis-Kaplan Executive Function System [Delis et al., 2001] that models the classic Stroop test [Stroop, 1935]. A subset of $n = 16$ SUD and $n = 9$ non-SUD participants completed the CWIT. This test requires inhibition of a prepotent word-reading response (e.g., the word "blue" printed in red letters). Scaled reaction time and error rate measures were used to index performance. Higher scores indicate better performance (shorter reaction times and fewer errors). Self-report measures of disinhibited real-world behavior were obtained with the "disinhibition" (DIS) subscale of the ESI. ESI-DIS items measure impulsive and/or irresponsible behaviors and traits (e.g., skipping work, failing to pay debts, and shoplifting), but do not explicitly involve substance use/abuse ("substance use" and "callous/aggressive" are separate subscales of the ESI).

Data analysis

To assess whether either cognitive-behavioral control measure was related to individual differences in connectivity, we regressed CWIT and ESI-DIS scores on connectivity estimates extracted from cortical clusters in which SUD and non-SUD groups had significantly different striatal connectivity. We reasoned that if the identified pattern of cortico-striatal connectivity were related to cognitive control processes, individual differences in connectivity between striatal ROIs and identified cortical regions would be related to psychological measures of cognitive control, across groups. However, to test whether the relationship between connectivity and behavior differed depending on SUD diagnosis, we also performed follow-up regression analyses modeling the interaction between group and behavior. To determine the specificity of any observed relationship between cortico-striatal connectivity and cognitive control, the same multiple regression procedure was used to examine the association between connectivity and more general measures of cognitive function (IQ and digit-span backward) and externalizing behavior (ESI callous/aggressive subscale). Group differences in cognitive control performance (CWIT) and self-reported behavioral disinhibition (ESI-DIS) were examined using Welch's two-sample t-tests.

RESULTS

rsFC Results

The three striatal seeds (Fig. 1A) yielded distinct but overlapping patterns of functional connectivity (Fig. 1B). Consistent with previous studies, the dorsal striatal seeds (caudate and putamen) had significant functional connectivity with more dorsal, lateral, and posterior areas of cortex than did the ventral striatum seed [Di Martino et al., 2008]. This general qualitative pattern was obtained in both the SUD and non-SUD groups. Relative to the non-SUD group, the SUD group exhibited significantly reduced functional connectivity between the NAc seed and four regions of cortex: the right frontal operculum (fO), left dorsal anterior cingulate cortex, and adjacent dorsomedial prefrontal cortex (hereafter referred to simply as dACC), left dorsolateral prefrontal cortex (dlPFC), and left inferior parietal lobule (IPL; Table II; Fig. 2A). As predicted, group differences in NAc connectivity corresponded to a network of brain regions previously implicated in cognitive-behavioral control [Corbetta and Shulman, 2002; Dosenbach et al., 2007; Miller and Cohen, 2001; Seeley et al., 2007]. We observed no significant group differences in connectivity for either of the dorsal striatal seeds (caudate and putamen). This pattern of results indicates reduced connectivity between NAc and brain regions involved in cognitive control in the SUD group.

Relationship Between rsFC Strength and Cognitive-Behavioral Control

As expected, the SUD group committed significantly more errors than the non-SUD group in the inhibition condition of the CWIT [$t(22.4) = 3.78$, $P = 0.001$], but not in the other two conditions, which did not require cognitive control [color naming: $t(17) = 0.47$, $P = 0.64$; word reading: $t(16.9) = 0.47$, $P = 0.65$]. There were no significant differences between SUD and non-SUD groups in the total completion time for any of the three CWIT conditions examined: color naming [$t(13.7) = 0.44$, $P = 0.66$], word reading [$t(12.7) = 0.83$, $P = 0.42$], and inhibition [$t(18.3) = 1.46$, $P = 0.16$]. Similarly, the SUD group scored significantly higher on the disinhibition subscale of the trait externalizing measure (ESI-DIS) than the non-SUD group [$t(22.7) = 3.89$, $P < 0.001$]. There were no significant group differences on the ESI callous/aggressive subscale [t(23.2)

TABLE II. Cortical regions with significant differences in NAc connectivity between SUD and non-SUD groups

Region	BA	Hemisphere	Coordinates: Peak T			T	Cluster Size
			x	y	z		
dlPFC (MFG)	9	L	−30	33	36	5.92	51
IPL	40	L	−51	−21	30	5.52	54
dACC	32	L/R	0	24	33	4.84	58
fO (IFG)	45/47	R	48	21	3	4.30	69

Coordinates are reported in Talairach atlas space. Cluster size indicates the number of contiguous voxels ($3 \times 3 \times 3$ mm^3). BA: Brodmann area; dACC: dorsal anterior cingulate cortex, dlPFC: dorsolateral prefrontal cortex, fO: frontal operculum, IFG: inferior frontal gyrus, IPL: inferior parietal lobe, MFG: middle frontal gyrus.

= 1.12, $P = 0.27$], highlighting the specificity of group differences to behavioral disinhibition. Together, these behavioral results are consistent with previous work linking SUD to poor behavioral control [Giancola and Moss, 1998; Li and Sinha, 2008; Lyvers, 2000; Mintzer and Stitzer, 2002].

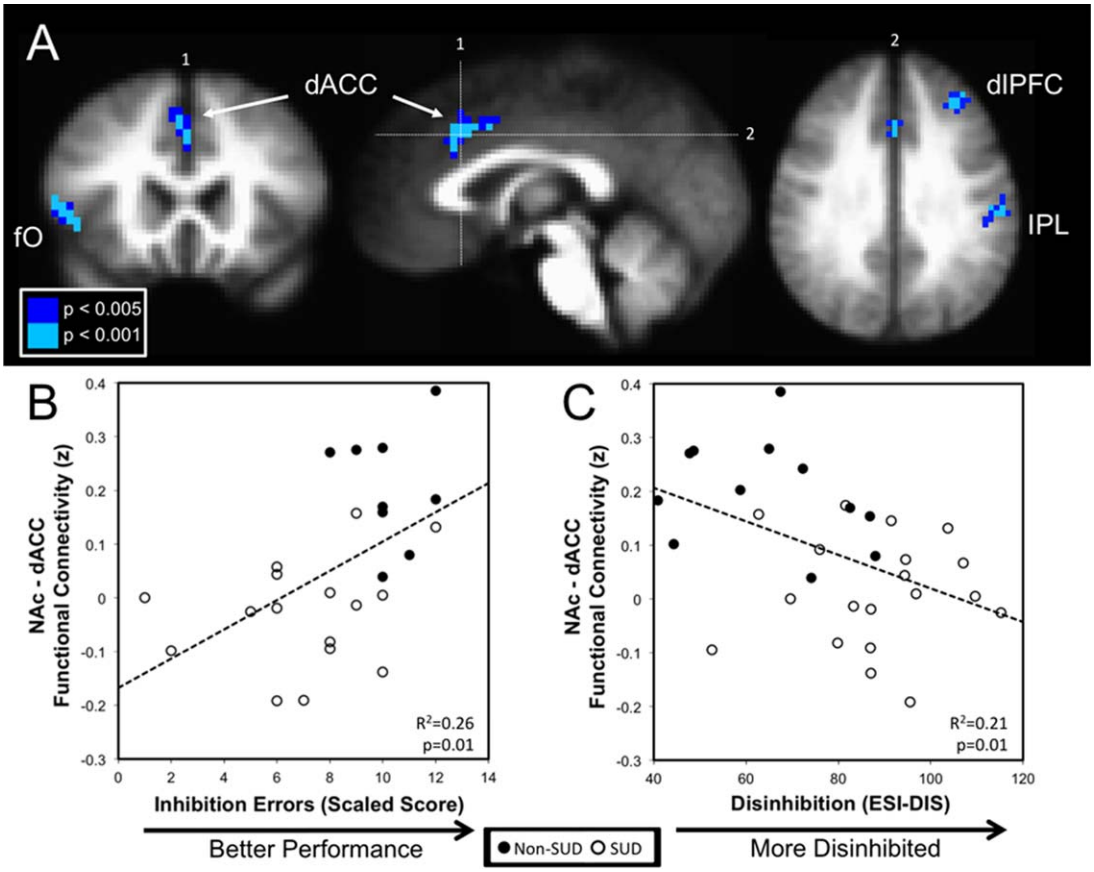

Figure 2.

Group differences in functional connectivity and relationship to cognitive-behavioral control. **A**: Group differences in connectivity based on the NAc seed ($P_{corrected} < 0.05$). The SUD group had significantly lower connectivity with four brain regions: fO, dACC, dlPFC, and IPL. Clusters are color-coded based on uncorrected P-values (dark blue: $0.001 < P < 0.005$; light blue: $P < 0.001$). **B**: Scatter plot depicting the relationship between scaled performance on the CWIT (higher scores indicate better performance) and z-transformed NAc connectivity with the dACC cluster. **C**: Scatter plot depicting the relationship between scores on the ESI-DIS subscale and z-transformed between NAc connectivity with the dACC cluster. Open circles: SUD participants; filled circles: non-SUD participants. Dashed lines represent the best-fit line across groups. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Across groups, functional connectivity between the NAc seed and the identified fO and dACC clusters was significantly correlated with the number of errors during CWIT inhibition, such that stronger connectivity was associated with fewer errors (Fig. 2B; fO: $r = 0.48$, $P = 0.02$; dACC: $r = 0.51$, $P = 0.01$). Similarly, functional connectivity between the NAc seed and each of the four identified clusters was negatively correlated with self-reported disinhibition (ESI-DIS), such that stronger connectivity was associated with lower disinhibition scores (Fig. 2C; fO: $r = 0.41$, $P = 0.02$; dACC: $r = 0.45$, $P = 0.01$; dlPFC: $r = 0.43$, $P = 0.01$; IPL: $r = 0.49$, $P = 0.005$). For neither measure (CWIT and ESI-DIS) did we observe a significant interaction between group and NAc functional connectivity (all P-values > 0.27), indicating that the brain-behavior correlations between rsFC and test performance did not differ between the SUD and non-SUD groups. Importantly, NAc functional connectivity with the cortical regions was unrelated to more general measures of intelligence and cognitive function (IQ and digit span backward; all P-values > 0.11) as well as other subscales of externalizing (callous/aggressive; all P-values > 0.13), highlighting the specificity of the relationship to psychological measures of cognitive-behavioral control. These findings support the hypothesis that individual differences in connectivity between the NAc seed and the cortical clusters derived from the between-groups analysis is related to individual differences in cognitive-behavioral control across groups.

Follow-Up Analyses

Psychopathy

In light of previous work associating psychopathy with altered patterns of functional connectivity [Ly et al., 2012; Motzkin et al., 2011], we performed separate whole-brain analyses covarying for psychopathy diagnosis (psychopath vs. non-psychopath) to determine whether psychopathy modulated SUD-related group differences. There were no significant interactions between psychopathy and SUD for any of the three striatal seeds, nor were there any group differences in connectivity between psychopathic and non-psychopathic inmates for these seeds. Further, when controlling for psychopathy, our main findings of altered connectivity between the NAc seed and each of the four identified clusters remained significant at the corrected threshold.

DISCUSSION

In this study, we used a combination of neuroimaging and behavioral analyses to demonstrate a distinct and behaviorally relevant pattern of circuit-level dysfunction in the brains of individuals with SUD. Relative to inmates without SUD, inmates diagnosed with SUD exhibited decreased functional connectivity between NAc and a network of cortical regions implicated in cognitive-behavioral control. Importantly, individual differences in NAc rsFC with these regions were related to individual differences in measures of cognitive-behavioral control, supporting the proposed behavioral relevance of the identified circuit. This convergence of functional brain imaging and behavioral results supports neuropsychological accounts of SUD that highlight deficient interactions between subcortical structures known to represent reward (NAc) and cortical areas involved in cognitive-behavioral control (fO, dACC, dlPFC, and IPL) [Baler and Volkow, 2006; Jentsch and Taylor, 1999; Koob and Volkow, 2010, Volkow et al., 2003].

The role of NAc in reward processing is well documented. NAc is a major target of mesolimbic dopamine neurons, which have been shown to signal the receipt and prediction of pleasurable, rewarding stimuli [Drevets et al., 2001; Schultz, 2010; Schultz et al., 1997]. Accordingly, human functional imaging studies have reliably demonstrated NAc activation in response to innately pleasurable stimuli (including drugs of abuse), as well as to abstract stimuli predicting their occurrence [Drevets et al., 2001; McClure et al., 2004; O'Doherty, 2004].

Likewise, a wealth of empirical data converge to implicate a network of interconnected cortical regions—comprised principally of dACC, fO, dlPFC, and lateral parietal cortex—as core neural substrates of cognitive-behavioral control [Dosenbach et al., 2007]. The dACC and fO exhibit highly correlated activity at rest and have been deemed critical nodes of an intrinsic salience network, involved in error-detection and performance monitoring [Botvinick et al., 1999; Carter et al., 1998; Dosenbach et al., 2006; Kerns et al., 2004; Mesulam and Mufson, 1982; Ridderinkhof et al., 2004; Seeley et al., 2007]. Activity in these regions is thought to signal the need for behavioral adaptation, recruiting prefrontal executive structures like the dlPFC and lateral parietal regions involved in attentional control [Braver et al., 2003; Corbetta and Shulman, 2002; Miller and Cohen, 2001; Selemon and Goldman-Rakic, 1988; Vincent et al., 2008]. Each of these prefrontal regions is known to have robust functional and structural connections with NAc [Cauda et al., 2011; Di Martino et al., 2008; Haber and Knutson 2010; Haber et al., 2006; Selemon and Goldman-Rakic, 1985]. Hence, the cortical regions exhibiting reduced connectivity with NAc in the SUD group in this study correspond directly to the cortical network previously implicated in cognitive-behavioral control.

Our psychological test data support this interpretation. Relative to the non-SUD group, the SUD group exhibited significantly poorer performance on a standard behavioral measure of cognitive control (inhibition errors on the CWIT) and reported a significantly greater degree of disinhibited real-world behavior on the ESI. Moreover, we observed significant correlations between performance on these behavioral measures and the strength of NAc connectivity with the identified cortical regions. In follow-up analyses modeling the interaction between group and behavior on NAc connectivity, we found no significant

interaction with group. Thus, although individual differences in NAc connectivity were significantly correlated with cognitive control measures across subjects, this association between NAc connectivity and cognitive control did not differ between SUD and non-SUD groups. It is interesting to note that the relationship with CWIT performance was only significantly related to connectivity with fO and dACC (regions specifically implicated in error monitoring), whereas self-reported disinhibition was related to connectivity with all four regions. To our knowledge, this is the first study linking NAc functional connectivity with psychological measures of cognitive-behavioral control. (Although, it should be noted that our approach of linking brain functional connectivity to cognitive task performance parallels a recent study of cocaine-dependent individuals in which perigenual ACC-lateral PFC connectivity was found to be correlated with performance on reversal learning and delay discounting tasks [Camchong et al., 2011]). There is a growing literature associating SUD with deficits in executive function and cognitive control using tasks, like the CWIT, that require inhibition of prepotent response tendencies [Giancola and Moss, 1998; Li and Sinha, 2008; Lyvers, 2000; Mintzer and Stitzer, 2002]. The dACC and dlPFC clusters identified in the present functional connectivity analysis are particularly notable for their overlap with regions shown to be hypoactive during a response inhibition task in cocaine users [Hester and Garavan, 2004; Kaufman et al., 2003]. The concordance of our rsFC and behavioral task results with previous fMRI-task data supports the assertion that the regions identified in the present between-groups analysis (fO, dACC, dlPFC, and IPL) are involved in cognitive-behavioral control, and moreover, that functional coherence between the NAc and these regions may be a neurobiological correlate of cognitive control efficacy that is compromised in SUD.

Interestingly, we did not observe any group differences in connectivity between the caudate or putamen seeds and any region of cerebral cortex. In light of the proposed role of these brain regions in mediating the compulsive, habitual drug taking behaviors that characterize the late stages of SUD, we might have predicted relative increases in connectivity between dorsal striatum and cortical regions involved in motor function, such as the primary motor cortex or cerebellum. The absence of group differences in connectivity with these regions may reflect the central importance of interactions between regions implicated in reward (NAc) and those implicated in cognitive control (e.g., fO, dACC, dlPFC, and IPL) in the development of SUD, or may simply reflect our unique sample characteristics. For example, it is possible that prolonged, enforced abstinence from drug use in the prison setting may have interrupted some of the habitual behaviors characteristic of long-term substance users (however, despite strict regulations against drug use in prison, several studies suggest that drugs of abuse may be commonly available to prisoners [Dolan et al., 2007; Gillespie, 2005]). It is also possible that the heterogeneity of drugs of abuse in our sample could obscure differences in dorsal striatum-mediated processes. The potential limitations of this study are discussed in greater detail below.

Ours is not the first study to examine rest-state NAc functional connectivity among individuals with SUD [Sutherland et al., 2012]. One recent study of chronic heroin users reported increased functional connectivity between NAc and rostral/ventral ACC (among other abnormalities), but no significant decrease in connectivity between NAc and the regions reported here [Ma et al., 2010]. The difference in results could be due to concurrent methadone treatment in the previous study (12 of the 14 heroin users were being treated with daily methadone at the time of fMRI data collection); methadone treatment has been shown to acutely reduce fMRI-BOLD activity in areas outside of ventral ACC among heroin-dependent individuals [Langleben et al., 2008]. However, similar increases in ventral ACC connectivity with a NAc seed were obtained in a study of chronic cocaine abusers [Wilcox et al., 2011]. A study of prescription opioid-dependent patients yielded a notably different pattern of results, finding decreased resting functional connectivity between NAc and rostral ACC, fO, and IPL, but not dACC or dlPFC [Upadhyay et al., 2010]. A separate study comparing cocaine users to non-drug users reported no significant group differences in resting functional connectivity using a NAc seed [Gu et al., 2010]. Thus, our study is the first to associate SUD with significantly reduced connectivity between NAc and the network of cognitive control regions reported here.

The divergence of the present results from previous findings may reflect methodological differences in our approach. Given the inconsistency of results in the extant literature prior to our study (none of the four previous studies revealed the same pattern of SUD-related group differences), we sought to systematically assess connectivity with three key striatal nuclei that have been widely implicated in neurocircuitry models of addiction [Everitt and Robbins, 2005; Koob and Volkow, 2010], and that have well-characterized and consistent connectivity patterns in healthy subjects [Di Martino et al., 2008; Postuma and Dagher, 2006]. In addition to the theoretical relevance of our chosen striatal seed regions, we elected to restrict our analysis to subcortical nuclei because they allow for more precise anatomical localization relative to cortical ROIs, which can vary significantly in functional organization across subjects [Feredoes et al., 2007]. Previous studies of striatal connectivity in SUD have been rather broad in their anatomical approach, assessing group differences in connectivity from several cortical and subcortical seeds simultaneously. These studies examined striatal connectivity in as few as four [Wilcox et al., 2011] or as many as ten [Ma et al., 2010] different cortical and subcortical seeds. Unlike this work, none of the previous studies corrected for multiple comparisons based on the number of seeds used in the functional connectivity analysis. Thus, our study has a more anatomically focused experimental

hypothesis and more stringent corrections for multiple comparisons than previous work on this topic.

The unique characteristics of our sample also warrant additional consideration. The SUD population studied here were prison inmates, some of whom had psychopathic personality. This population may have especially pronounced deficits in cognitive-behavioral control related to their substance use problems. Without a separate comparison population of non-incarcerated SUD participants, we are unable to determine whether the patterns of functional connectivity observed here relate only to this specific population or to SUD more generally. However, groups were well-matched for psychopathy diagnosis (Table I) and follow-up whole-brain connectivity analyses covarying for psychopathy revealed identical SUD-related group differences, indicating that psychopathy likely did not contribute to our observed results. Additionally, our sample diverges from previous studies in the heterogeneity of drug use in the SUD group; the majority of our SUD sample met the criteria for dependence on more than one substance. Thus, whereas previous studies may be observing substance-specific neurobiological differences, our results may reflect neurobiological differences that are common across different substances of abuse, or related specifically to polysubstance abuse—although it is also possible that our findings are driven primarily by participants with abuse or dependence on alcohol (n = 20/22 SUD participants) and/or cannabis (n = 18/22 SUD participants). Another limitation of this study is the lack of data on nicotine use, which has previously been associated with changes in brain functional connectivity [Cole et al., 2010; Hong et al., 2009, 2010]. It is possible that differences in current and/or past nicotine use could have contributed to our findings. However, given that nicotine is itself an addictive substance of abuse and that the majority of our SUD sample are polysubstance abusers anyway, allowing that nicotine use could contribute to the observed rsFC data does not appreciably alter the basic findings of this study. Future work in larger samples will be necessary to distinguish the neurobiological and psychological mechanisms related to individual substances from those that are common across substances.

Finally, although the behavioral data strongly support our assertion that NAc connectivity with the cortical regions identified here is related to cognitive-behavioral control, this design is not well suited to investigate the possibility of breakdowns in the brain-behavior relationship in individuals with SUD. In other words, it is possible that SUD involves a disruption in the typical association between neurobiological indices of brain function and behavior (which would present as a significant interaction with group in our regression analyses). Although we found no significant interaction with group for cortical clusters identified in the whole-brain between-groups analysis (indicating that the relationship between connectivity and behavior did not differ between groups for these regions), there may be other brain regions and psychological functions for which the relationship between connectivity and behavior is divergent in SUD. Future work investigating interactions between group, functional connectivity, and other domains of SUD-relevant psychological functions (e.g., reward processing) at the whole-brain level will be required to examine such a hypothesis.

In conclusion, the results reported here associate SUD with reduced functional connectivity between NAc and a network of cortical regions including the fO, dACC, dlPFC, and lateral parietal cortex. Importantly, this circuit-level neural dysfunction relates to deficits in behavioral inhibition. Despite extensive convergent evidence for local dysfunction within dorsal striatum in SUD, we did not observe any circuit-level differences in either dorsal caudate or putamen in this study. Thus, our results highlight the key role of cognitive-behavioral control processes relevant to reward in SUD. Although remarkably consistent with extant models of neuropathology in SUD, our results reveal heretofore unidentified SUD-related differences in functional connectivity between the NAc and frontal executive structures. Future research in larger populations with and without polysubstance abuse and subsequent meta-analysis will be essential for disentangling the functional changes most critical for developing SUD from those more specific to particular substance-using populations. Nonetheless, the present findings underscore a key role for disrupted connectivity between the subcortical structures implicated in reward processing and frontal executive structures implicated in cognitive-behavioral control in SUD pathology, providing a neuropsychological framework for future research.

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