Published in final edited form as:

Am J Drug Alcohol Abuse. 2013 November ; 39(6): . doi:10.3109/00952990.2013.841711.

A preliminary investigation of Stroop-related intrinsic connectivity in cocaine dependence: Associations with treatment outcomes

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Abstract

Background—Cocaine-dependent individuals demonstrate neural and behavioral differences compared to healthy comparison subjects when performing the Stroop color-word inference test. Stroop measures also relate to treatment outcome for cocaine dependence. Intrinsic connectivity analyses assess the extent to which task-related regional brain activations are related to each other in the absence of defining a priori regions-of-interest.

Objective—This study examined: 1) the extent to which cocaine-dependent and non-addicted individuals differed on measures of intrinsic connectivity during fMRI Stroop performance; and, 2) the relationships between fMRI Stroop intrinsic connectivity and treatment outcome in cocaine dependence.

Methods—Sixteen treatment-seeking cocaine-dependent patients and matched non-addicted comparison subjects completed an fMRI Stroop task. Between-group differences in intrinsic connectivity were assessed and related to self-reported and urine-toxicology-based cocaine-abstinence measures.

Results—Cocaine-dependent patients vs. comparison subjects showed less intrinsic connectivity in cortical and sub-cortical regions. When adjusting for individual degree of intrinsic connectivity, cocaine-dependent vs. comparison subjects showed relatively greater intrinsic connectivity in the ventral striatum, putamen, inferior frontal gyrus, anterior insula, thalamus, and substantia nigra. Non-mean-adjusted intrinsic-connectivity measures in the midbrain, thalamus, ventral striatum, substantia nigra, insula, and hippocampus negatively correlated with measures of cocaine abstinence.

Conclusion—The diminished intrinsic connectivity in cocaine-dependent vs. comparison subjects suggests poorer communication across brain regions during cognitive-control processes. In mean-adjusted analyses, the cocaine-dependent group displayed relatively greater Stroop-related connectivity in regions implicated in motivational processes in addictions. The

relationships between treatment outcomes and connectivity in the midbrain and basal ganglia suggest that connectivity represents a potential treatment target.

Keywords

intrinsic connectivity; cocaine dependence; functional magnetic resonance imaging; Stroop color-word interference test; treatment outcome; addiction; cognitive control

INTRODUCTION

Cocaine-dependent individuals differ from non-addicted subjects on measures of cognitive control. For example, cocaine-dependent subjects have been found to perform poorly on the Stroop color-word interference test, a widely used cognitive-control task (1). Stroop performance has been linked to treatment outcome in cocaine-dependent patients (2), suggesting that individual differences in inhibiting prepotent responses may relate importantly to clinical response. In functional magnetic resonance imaging (fMRI) studies of Stroop performance in cocaine dependence, frontal cortical and midbrain activations underlying cognitive control have been associated with treatment outcome (2–6). In an fMRI study, pre-treatment Stroop-related neural activity in the striatum, ventromedial prefrontal cortex and cingulate cortex was associated with self-reported and/or urine-toxicology-based measures of cocaine abstinence (5). A subsequent study of substance-abusing individuals (including cocaine-dependent subjects) receiving behavioral therapy demonstrated decreased Stroop-related BOLD signal post-treatment relative to pre-treatment in the anterior cingulate, right inferior frontal gyrus, dorsolateral prefrontal cortex, and midbrain (7). In addition, the substance-abusing group showed a greater decrease in Stroop-related activity in the subthalamic nucleus, midbrain, and surrounding areas in post-treatment compared to both pre-treatment and healthy comparison subjects following test-retest (7). Taken together, these findings suggest that brain activity underlying cognitive control relate importantly to, and may be changed during, treatments for addictions.

As brain regions operate in circuits, understanding how circuitry function relates to treatment outcome may shed light on neural mechanisms underlying specific therapies or the process of recovery in general. Functional-connectivity-based analytic strategies may be used to examine relationships between neural circuits and treatment outcomes. Multiple methods exist for investigating functional connectivity. Independent component analysis (ICA) can use spatial patterns of signal changes to identify functionally integrated activations or circuits ((8–10); reviewed in (11)). Our group's ICA study of cocaine-dependent and comparison subjects performing the fMRI Stroop task identified five functional networks involving cingulate, frontal and subcortical regions (6). Greater engagement of subcortical (involving limbic structures and left inferior frontal cortex) and ventral fronto-striatal (involving ventromedial prefrontal cortex, ventral striatum and rostral anterior cingulate) networks during incongruent versus congruent stimuli presentation was associated with greater abstinence during treatment (6).

To further study functional connectivity in cocaine dependence, we examined brain activity from cocaine-dependent and healthy comparison subjects using a recently developed approach that assesses intrinsic connectivity. Unlike some forms of connectivity analyses that depend upon pre-identified regions of interest (e.g., dynamic causal modeling or “seed-based” approaches (12–16); reviewed in (17)), intrinsic connectivity reflects tissue functional connectivity using a whole-brain approach without restricting analyses to a priori regions of interest (18).

Given the effects of cocaine on brain structure and function (19), we hypothesized that we would observe less overall intrinsic connectivity in cocaine-dependent patients than in healthy comparison subjects during Stroop performance. Given our ICA findings (6), we further hypothesized that after adjusting for individual differences in degree of whole-brain intrinsic connectivity, cocaine-dependent individuals would display relatively greater connectivity in brain regions (e.g., ventromedial prefrontal cortex, striatum, and insula) implicated in addiction and in Stroop performance in previous fMRI work (6, 20). We also hypothesized that in the cocaine-dependent group, treatment outcomes would relate to Stroop-related intrinsic-connectivity measures in regions previously implicated in cocaine treatment outcomes, including the ventromedial prefrontal cortex, cingulate cortex, and striatum (5).

METHODS

Participants

The protocol was reviewed and approved by Yale's institutional review board. All participants provided written informed consent. Sixteen cocaine-dependent individuals and 16 healthy comparison subjects were recruited and matched on socio-demographic measures were studied (although one cocaine-dependent and one healthy comparison subject were subsequently excluded [see below]) (see Table 1). Cocaine-dependent subjects were treatment-seeking adults recruited from an outpatient treatment center and whose primary drug was cocaine (several subjects were additionally methadone maintained, $n=3$). Subjects were excluded if they met DSM-IV criteria for psychotic or bipolar disorders, but not for antisocial personality disorder, major depressive disorder, or a substance-induced mood disorder. Psychiatric diagnoses were assessed using the Structural Clinical Interview for DSM-IV (SCID) (21, 22). Healthy comparison subjects were also assessed using the SCID and were excluded for any psychotic, bipolar or substance-use disorders (except possible nicotine dependence). Subjects were participating in 8-week or 12-week clinical trials of behavioral and/or pharmacological therapies as follows: cognitive behavioral therapy alone, $n=8$; treatment as usual, $n=5$; contingency management + cognitive behavioral therapy, $n=1$; disulfiram + cognitive behavioral therapy, $n=2$ (for more information and treatment outcomes of clinical trials see (7, 23)). Subjects were selected from larger samples of cocaine-dependent and comparison subjects based on similar socio-demographic measures (to create groups not differing on measures of age, gender and race/ethnicity). Several subjects' data have been previously used in fMRI studies using statistical-parametric-modeling (SPM) or ICA approaches (5–7, 24). All scans were performed at baseline, prior to randomization and initiation of treatment. Two within-treatment cocaine-use treatment-outcome measures were included in analyses: 1) percent of cocaine-positive urines; and, 2) longest duration of cocaine abstinence. Percent cocaine-positive urines, calculated by dividing the number of cocaine-positive urines by the total number of urine specimens provided during active treatment, is a widely used biological indicator of within-treatment cocaine use and shows strong associations with longer-term abstinence outcomes (25, 26). Longest duration of cocaine abstinence, reflecting the longest continuous cluster of self-reported days of cocaine abstinence during active treatment as assessed using the Timeline Followback method (27), is also strongly associated with longer-term clinical outcomes across multiple trials (25, 26, 28).

Within the cocaine-dependent group, several individuals reported use of substances other than cocaine in the month prior to treatment (Table 1), meeting criteria for primarily alcohol- and cannabis-use disorders. In addition to substance-use disorders, DSM-IV criteria were met for antisocial personality disorder ($n=3$), current ($n=1$) or lifetime ($n=2$) substance-induced mood disorder and lifetime major depression ($n=7$). Fifteen cocaine-dependent subjects and three healthy comparison subjects were current daily tobacco smokers, and one

cocaine-dependent subject smoked tobacco occasionally throughout the month prior to treatment initiation.

Two subjects, one from each group, were removed from all analyses as they exhibited excess motion (greater than 2 mm displacement and/or 3 degrees of rotation) during fMRI scanning (resulting in a n=15 in each group for fMRI analyses; we subsequently will refer to these 30 subjects only in analyses). Due to a technical recording malfunction, verbal Stroop response times were not available for 8 subjects (4 cocaine-dependent (n=11) and 3 healthy comparison (n=12) subjects). Treatment outcome data were not available for the 3 methadone-maintained individuals (as this is an ongoing trial) of the treatment-seeking cocaine-dependent patients (leaving n=12). Individuals with missing treatment outcome or Stroop behavioral data were excluded from the respective analyses.

fMRI Stroop Task

Subjects performed the Stroop task as previously described (5, 7). Briefly, participants were shown a color-word (e.g., “BLUE”) that was printed in either a congruent (e.g., blue) or an incongruent (e.g., green) color. Subjects completed two practice runs prior to scanning, with tobacco smokers given the opportunity to smoke a cigarette about an hour prior to scanning in order to avoid acute effects of tobacco or tobacco withdrawal during fMRI. During scanning, word stimuli were presented on the screen for 1300msec with a 350msec inter-trial interval with incongruent stimuli pseudo-randomly presented every 13th–16th congruent stimuli. There were seven incongruent events in each run, and participants completed a total of 6 runs with 105 stimuli (5). Behavioral Stroop performance was assessed out-of-scanner during five runs presented immediately following scanning. A microphone recorded verbal responses as reaction times on each trial, and errors on incongruent trials were recorded by research staff. While performing the in-scanner Stroop task, participants were asked to silently name the color to avoid motion associated with speech and reduce working memory load related to translating mental/verbal responses to motor responses. This version of the Stroop has been found to show similar patterns of brain activations as have other cognitive control tasks that involve in-scanner responses (e.g., the Simon – (29)) and has been used in our previously published work (5–7, 20, 29).

Image Acquisition

Images were obtained with a Siemens Trio 3T magnetic resonance imaging (MRI) system (Siemens AG, Erlangen, Germany). Localizer images were acquired for prescribing the functional image volumes, aligning the seventh or eighth slice parallel to the plane transecting the anterior and posterior commissures. Functional images were collected using an echo-planar image gradient echo pulse sequence (TR=1500ms, TE=27ms, FoV=220mm, matrix size=64×64, slice thickness=5mm, Flip Angle=60°, Bandwidth=2520Hz/pixel, 124 volumes with 25 slices). Functional runs consisted of 124 volumes (approximately 3 min scan length) with the first six volumes discarded to allow the magnetization to reach the steady-state. T1-weighted 2D anatomical images were collected (TR=300ms, TE=2.47ms, FoV=220mm, matrix size=256×256, slice thickness=5mm, Flip Angle=60°, Bandwidth=300Hz/pixel with 25 slices) with 25 AC-PC aligned axial-oblique slices in addition to 3D anatomical scans using Magnetization Prepared Rapid Gradient Echo (MPRAGE) (176 contiguous sagittal slices, slice thickness=1mm, matrix size=256×256, FoV=256mm, TR=2530ms, TE=2.77, Flip Angle=7°, Bandwidth=179Hz/pixel). After these structural images, acquisition of functional data began in the same slice locations as the axial-oblique T1-weighted data.

fMRI Analysis

Data analyses were performed as previously described (18). Briefly, images were slice-time-corrected using sinc interpolation and motion-corrected using SPM5 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm5/>). All further analyses were performed using BioImage Suite (30). Several covariates of no interest were regressed from the data including linear and quadratic drift, six rigid-body motion parameters, mean cerebral-spinal-fluid (CSF) signal, mean white-matter signal, and overall global signal. Finally, a gray-matter mask was applied to the data so only voxels in the gray matter were used in the calculation.

After preprocessing, the six Stroop task runs were concatenated and the functional connectivity of each voxel, as measure by the intrinsic connectivity distribution (ICD), was calculated for each individual subject as described previously (18). Similar to most voxel-based functional connectivity measures (31), ICD involves correlating the time course for any given gray-matter voxel with the time course of every other gray-matter voxel in the brain, and then summarizing these correlations with a network theory metric. Specifically, ICD models the entire distribution of the network measure of degree, therefore eliminating the need to specify a connection threshold. Because the removal of the global mean makes the signs of the correlations ambiguous, we only focus on the positive correlations (32). A histogram of these positive correlations was constructed to estimate the distribution of connections to the voxel in question. This distribution of connections was converted to a survival function and the survival function was fitted with a stretched exponential with unknown variance, $y = Ae^{-Bx^C}$. As alpha controls the spread of the distribution of connections, a larger alpha indicates a greater number of high correlation connections. Finally, this process is repeated for all voxels in the gray matter resulting in a parametric image of the alpha parameter for each subject, which was used in all between group and correlational analyses.

Additionally, to interrogate relative differences in connectivity, each subject's map was normalized by subtracting that subject's mean across all voxels and dividing by the standard deviation across all voxels (henceforth be referred to as mean-adjusted) to be used in the between group analysis. This z-score-like normalization does not change the underlying connectivity pattern but allows for investigation of relative differences in connectivity in the presences of large global differences connectivity. Finally, all single subject results were spatially smoothed with a 6mm Gaussian filter and warped to a common template space through the concatenation of a series of linear and non-linear registrations.

Voxel-wise, two-sample t-tests were used to compare intrinsic connectivity between the cocaine-dependent and healthy comparison groups. To examine the association between intrinsic connectivity across the whole brain during fMRI Stroop performance with treatment outcome measures in the cocaine-dependent group, a voxel-wise correlation analysis was conducted. Significance was assessed at a voxel-level threshold of $p < 0.05$ with a conjoint cluster threshold of 163 voxels corresponding to a $p < 0.05$ family-wise error (FWE) correction as determined by AFNI's AlphaSim program.

Motion Analysis

As group differences in motion have been shown to confound functional connectivity results, average frame-to-frame displacement was calculated for each group (33). There were no significant group differences in motion between cocaine-dependent and healthy comparison subjects ($t = 0.63$; $p > 0.53$).

Demographic Analysis

Statistical analyses to compare groups on baseline and demographic variables were conducted using SPSS 19.0. Paired samples t-tests were used to determine differences between cocaine-dependent and healthy comparison groups on continuous variables (i.e. age). Chi-squared tests were used to determine differences between groups on categorical variables (i.e. gender).

Behavioral Stroop Analysis

Differences in Stroop performance between cocaine-dependent and healthy comparison groups were analyzed using a mixed ANOVA model. Differences in Stroop performance within cocaine-dependent and healthy comparison groups were analyzed using paired samples t-tests. Pearson correlations were used to determine the relationships between behavioral Stroop performance and treatment outcomes measures in cocaine-dependent participants.

RESULTS

Participants

Participant characteristics of the 15 subjects from each diagnostic group used in MRI analyses are summarized in Table 1. The cocaine-dependent and healthy comparison groups did not significantly differ in age ($t=-0.30$, $p=0.77$), gender ($\chi^2=0.54$, $p=0.46$), race/ethnicity ($\chi^2=1.86$, $p=0.39$), or education (completion of high school vs. did not complete high school) ($\chi^2=2.14$, $p=0.14$). There was a significant difference in IQ between cocaine-dependent and healthy comparison subjects (cocaine-dependent: Mean $\pm$ SD=87.33 $\pm$ 12.84; healthy comparison: 107.25 $\pm$ 9.77; $t=-4.06$, $p<0.001$). For cocaine-dependent subjects, substance use in the past month and lifetime is listed in Table 1.

fMRI Intrinsic Connectivity

Whole-brain contrast maps show a significant difference in Stroop-related intrinsic connectivity between cocaine-dependent and healthy comparison groups, such that the cocaine-dependent group displayed less intrinsic connectivity in the frontal cortices (including the anterior cingulate and posterior cingulate), inferior frontal gyrus, insula, caudate, thalamus, amygdala, and hippocampus (Figure 1; Table 2). When the results were adjusted for individual differences in connectivity across the whole brain, relatively greater mean-adjusted intrinsic connectivity was identified in cocaine-dependent versus healthy comparison groups in the right caudate, bilateral orbitofrontal cortex, inferior frontal gyrus, insula, thalamus, substantia nigra, and ventral striatum (Figure 2; Table 3).

Several post-hoc analyses were conducted in order to determine the potential influences of major depressive disorder, prior chronic opiate use, and IQ on intrinsic connectivity findings. As compared to the findings described above and shown in Supplemental Figure S1a, in non-mean-adjusted connectivity maps removing individuals with major depressive disorder ($n=6$), a less extensive pattern of intrinsic-connectivity differences was observed (Supplemental Figure S1b). When individuals with prior chronic opiate use ($n=7$) were excluded, a more extensive pattern of between-group differences in non-mean-adjusted intrinsic connectivity was observed (Supplemental Figure S1c versus S1a). In the mean-adjusted maps, less extensive changes were observed than in the non-mean-adjusted maps (Supplemental Figure 2). In analyses excluding individuals with depression (Supplemental Figure S2b), the left anterior insula was no longer implicated and in analyses excluding those with chronic opiate use, a largely similar pattern of between-group differences was observed; however the pattern of between-group differences is slightly more extensive when opiate users are excluded (Supplemental Figure S2c versus S2a).

In analyses adjusting for IQ, a less robust pattern of between-group differences was observed in the non-mean adjusted maps (Supplemental Figure S1d versus S1a). In the mean-adjusted maps, fewer between-group differences were observed from the non-IQ-adjusted map, with the most substantial difference being that the ventral prefrontal cortex/orbitofrontal cortex was no longer implicated (Supplemental Figure S2d versus S2a).

Behavioral Stroop Data

A two-factor mixed ANOVA (trial type [incongruent or congruent] $\times$ group [cocaine-dependent or healthy comparison]) revealed a significant main effect of trial type ($F_{(1,21)}=173.38$, $p<0.0001$), but no main effect of group ($F_{(1,21)}=0.06$, n.s.), suggesting that cocaine-dependent and healthy comparison groups did not show a differential Stroop effect (incongruent minus congruent response times). Paired-samples t-tests showed significantly slower response times to incongruent relative to congruent trials in both cocaine-dependent and healthy comparison groups ($t=-8.52$, $p=0.0001$; $t=-10.36$, $p=0.0001$, respectively), indicating that both groups demonstrated the expected 'Stroop effect', consistent with greater interference during incongruent trials (congruent trials: cocaine-dependent: Mean $\pm$ SD=593.68 $\pm$ 73.57msec; healthy comparison: 592.20 $\pm$ 110.96msec; incongruent trials: cocaine-dependent: 836.32 $\pm$ 148.01msec; healthy comparison: 812.63 $\pm$ 170.98msec). There were no differences between cocaine-dependent and healthy comparison groups in reaction time for either congruent ($t=0.37$, n.s.) or incongruent ($t=0.35$, n.s.) trials. In addition there were no differences in the number of errors made on incongruent trials between cocaine-dependent and healthy comparison groups ($t=0.27$, n.s.; cocaine-dependent: Mean $\pm$ SD=5.73 $\pm$ 5.98; healthy comparison: 5.08 $\pm$ 5.30). There was no relationship between IQ and performance on the Stroop task ($F_{(1,18)}=1.15$; n.s.). Additionally, there were no relationships identified between measures of Stroop behavioral performance and intrinsic connectivity (non-mean-adjusted or mean-adjusted) in whole-brain analyses thresholded at $p<0.05$ FWE-corrected.

Relationships Between Behavioral Stroop Measures and Treatment Outcome in Cocaine Dependence

Mean incongruent response times and the Stroop effect were positively correlated with the maximum number of self-reported days of consecutive abstinence from cocaine during treatment ($r=0.73$, $p<0.05$; $r=0.78$, $p<0.05$, respectively) and Stroop effect was marginally negatively correlated with the percent of positive urine samples ($r=-0.66$, $p<0.05$). These results suggest greater interference at pretreatment was associated with better treatment outcomes.

Relationships Between Non-mean-adjusted Intrinsic Connectivity and Treatment Outcome in Cocaine Dependence

Non-mean-adjusted intrinsic connectivity involving the bilateral thalamus, ventral striatum, and substantia nigra regions was negatively correlated with the maximum number of self-reported days of consecutive abstinence from cocaine during treatment (Figure 3a, Table 4A). Non-mean-adjusted intrinsic connectivity involving the bilateral thalamus, ventral striatum, substantia nigra, right insula, and left hippocampus was positively correlated with the percent of positive urine screens (Figure 3b, Table 4B). Therefore, greater non-mean-adjusted intrinsic connectivity involving these regions was associated with worse within-treatment cocaine-use outcomes.

DISCUSSION

In this preliminary investigation applying intrinsic-connectivity analyses to fMRI Stroop data, cocaine-dependent versus healthy comparison participants showed a more diffuse

pattern of diminished intrinsic connectivity involving cortical and subcortical structures. However, when data were mean-adjusted to each subject's mean connectivity, the cocaine-dependent group showed relatively greater intrinsic connectivity in the frontal cortices (including the OFC, anterior and posterior cingulate, and inferior frontal gyrus), insula, thalamus, and amygdala. Taken together, these data suggest that cocaine-dependent patients have less intrinsic connectivity overall yet may rely on greater recruitment of specific regions or circuits during situations involving cognitive conflicts or requiring greater cognitive control. Additionally, less Stroop-related intrinsic connectivity in the ventral striatum, thalamus, substantia nigra, right insula, and left hippocampus was associated with greater abstinence during treatment as measured by self-report and urine toxicology. These findings extend our prior results (5, 6) and suggest that relatively greater connectivity within limbic, ventral cortical and cingulate regions relate prospectively to poor treatment response among cocaine-dependent individuals.

Intrinsic Connectivity

As hypothesized, cocaine-dependent patients displayed less overall intrinsic connectivity as compared with healthy comparison participants during Stroop performance. Similar findings of diminished connectivity within cocaine-dependent compared with healthy comparison subjects have been reported using other approaches to measuring functional connectivity at resting state, during moral judgment tasks, and during language processing (34, 35). Tomasi et al. (36) investigated functional connectivity within the midbrain in cocaine-dependent compared with healthy comparison individuals during a sustained attention task. In this study, cocaine-dependent subjects had lower functional connectivity and diminished connectivity between the midbrain and the thalamus, cerebellum, and rostral cingulate regions was associated with diminished task-related activity in these regions. These data suggest that decreased functional connectivity within the midbrain can disrupt cognitive processes such as sustained attention. Resting state studies also find alterations in functional connectivity in addicted individuals (37–39). Taken together, these studies provide evidence for decreased connectivity within cocaine-dependent versus healthy comparison subjects during cognitive tasks and at rest.

In contrast, greater intrinsic connectivity was observed in the mean-adjusted maps, which may signal a relatively greater recruitment of these brain regions in cocaine-dependent subjects as cognitive demands increase. Greater intrinsic activity in the fronto-thalamic regions in cocaine dependent individuals may reflect more difficulty in inhibitory control. In support of this idea, the inferior frontal gyrus and anterior insula have been implicated in cognitive control and emotional processing (40). The inferior frontal gyrus (particularly in the right hemisphere) is activated in tasks testing inhibitory control (41–45). In humans and monkeys, lesions or damage to the inferior frontal gyrus has been shown to disrupt inhibition (46, 47), which can then impair other measures of executive function. In addition, the orbital frontoinsula region has been proposed as a central component of a salience-processing network involving the thalamus, substantia nigra, and putamen (48). Therefore, increased connectivity within these regions as observed in the current study may suggest heightened salience and motivational processing. If these processes contribute to maintenance of addictive processes (49), greater connectivity in these areas might be expected in cocaine-dependent individuals who are less responsive to treatment.

The finding that less non-mean-adjusted intrinsic connectivity between the ventral striatum, thalamus, substantia nigra, right insula, and left hippocampus was associated with greater abstinence during treatment is noteworthy as many of these areas are encompassed by the basal ganglia, regions heavily implicated in cognitive and emotional processes, reward and reinforcement, addictive behaviors, and habit formation (50–53). A recent study investigated fMRI brain reactions to high-calorie food cues in obese individuals as a predictor of weight-

loss treatment (54). Many of the same brain regions involved in motivational/salience processing (ventral striatum, substantia nigra, thalamus, and insula) were negatively associated with treatment outcome, such that greater activation to food cues in these regions was predictive of poorer treatment outcome (54). Together, the current and extant findings suggest that motivational/salience processing is disrupted in cocaine-dependent individuals, and greater connectivity within these regions may reflect a deficit in motivational flexibility. Thus, individuals with greater intrinsic connectivity within these regions may experience greater difficulty reversing over-active reward-seeking (i.e. drug-seeking) behavior to maintain abstinence.

Post-hoc analyses explored the potential contributions of major depression, chronic opiate use and IQ. Although differences were identified (albeit fewer with respect to opiate use), these should be interpreted with caution, particularly as some differences might relate to diminished power with reduced sample sizes. However, the possibilities that depression and IQ might account in part for individual differences in diffuse connectivity warrants additional direct examination in larger samples. Additionally, the possibility that depression in cocaine dependence might influence relative network connectivity with the insula, a brain region implicated in interoceptive processing, drug craving and cognitive control associated with relapse (55–57), warrants additional investigation, as does the possibility that IQ may in part account for relative connectivity with the ventral prefrontal/orbitofrontal cortex. Given findings implicating this region in decision-making in substance dependence (58), further direct examination of how IQ influences function of brain circuits involving the ventral prefrontal cortex/orbitofrontal cortex is warranted. Although these findings may be robust given the noticeable differences in exploratory maps investigating the possible influences of depression and IQ, interpretation should be tempered by the small sample in the current study.

Strengths and Limitations

Strengths of this study include the use of a relatively novel intrinsic connectivity approach. This approach has the advantages of not relying on a priori seeds or regions of interest and characterizing the distribution of connections across all thresholds, thus eliminating the need to choose a threshold for analysis. A second advantage is the application of the approach to Stroop fMRI data. Performance on the Stroop has been associated with clinically relevant measures such as treatment outcome (2) and functional networks which underlie Stroop performance as identified by an independent approach (independent component analysis) have been associated with treatment outcome in cocaine-dependent patients (6). This study thus adds to a small yet growing literature investigating functional networks in cocaine-dependent individuals and their relationships to treatment outcome with an eye towards and the development of more effective treatments (see (59)).

This study used a clinical treatment-seeking population; a caveat of such a population is that many of the subjects also used drugs other than cocaine. Thus, while patients identified cocaine as their primary drug, differences in intrinsic connectivity may not relate entirely or directly to cocaine use. Possible influences of other drugs (e.g., tobacco) warrant additional investigation. Given the cross-sectional nature of the study, it is also unclear the extent to which the observed differences in intrinsic connectivity may have been pre-existing (prior to any cocaine use) or developed during the course of the disorder.

There are several additional limitations. The samples are small, and some behavioral and treatment outcome data were not available. The samples in the post-hoc analyses were particularly small, and more studies should investigate in larger samples the potential influences of individual differences (e.g., relating to depression and IQ) on findings in cocaine dependence (e.g., on Stroop performance and brain function). Some of the fMRI

Stroop data have also been used in prior studies using other analytical approaches (e.g., SPM and ICA) (5–7, 24). While all cocaine-dependent subjects were recruited from an outpatient treatment center, they were not all undergoing the same treatment. Subjects were selected from three different treatments involving behavioral and/or pharmacological therapies of either 8 or 12 weeks in duration (see Methods for more details). Cocaine-dependent and healthy comparison subjects were not matched on IQ and the cocaine-dependent subjects scored significantly lower on the Shipley IQ test than healthy comparison subjects. While similar findings have been reported in other studies (60–63), IQ may account for some of the connectivity findings and future studies should further investigate the influence of IQ. The fMRI Stroop task does not collect in-scanner performance information and thus does not allow for the analysis of in-scanner error trials. In addition, there were microphone malfunctions which reduced the sample size and may have reduced the ability to detect relationships between behavioral Stroop performance and intrinsic connectivity. Data were also analyzed only at pre-treatment and future studies with larger samples should investigate intrinsic connectivity measures over the course of treatment and after treatment completion.

This study expanded on previous research of cognitive control in cocaine dependence using the Stroop task by investigating intrinsic connectivity differences between cocaine-dependent and healthy comparison subjects. There was lower overall intrinsic connectivity in cocaine-dependent as compared with healthy comparison individuals. However, when these data were adjusted to each subject's individual intrinsic connectivity mean, cocaine-dependent subjects displayed relatively greater intrinsic connectivity within the frontal cortex and basal ganglia. In addition, greater intrinsic connectivity within regions of the midbrain and basal ganglia was associated with less successful abstinence outcomes during treatment. These preliminary findings provide a foundation for future research investigating the mechanisms underlying cocaine dependence and its treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Disclosure of the sources of any support for the work, received in the form of grants and/or equipment and drugs:

Supported by: P50DA09241 (KMC), R01DA020908 (MNP), P20DA027844 (MNP), R01EB009666 (RTC), Connecticut Department of Mental Health and Addiction Services, and the Connecticut Mental Health Center. E.E. DeVito is supported by K12DA031050 (Mazure, PI) from NIDA, NIAAA, Office of Research on Women's Health (ORWH) and NIH Office of the Director (OD). M.R. Mitchell is supported by T32DA007238 (Petrakis, PI).

The authors report no conflicts of interest. Dr. Potenza has received financial support or compensation for the following: Dr. Potenza has consulted for and advised Boehringer Ingelheim, Lundbeck and Ironwood; has financial interests in Somaxon; has received research support from the National Institutes of Health, Veteran's Administration, Mohegan Sun Casino, the National Center for Responsible Gaming and its affiliated Institute for Research on Gambling Disorders, and Forest Laboratories pharmaceuticals; has participated in surveys, mailings or telephone consultations related to drug addiction, impulse control disorders or other health topics; has consulted for gambling and legal entities on issues related to addictions or impulse control disorders; has provided clinical care in the Connecticut Department of Mental Health and Addiction Services Problem Gambling Services Program; has performed grant reviews for the National Institutes of Health and other agencies; has guest-edited journal sections; has given academic lectures in grand rounds, CME events and other clinical or scientific venues; and has generated books or book chapters for publishers of mental health texts.

REFERENCES

1. MacLeod CM. Half a century of research on the Stroop effect: an integrative review. *Psychological bulletin*. 1991; 109(2):163–203. [PubMed: 2034749]

2. Streeter CC, Terhune DB, Whitfield TH, Gruber S, Sarid-Segal O, Silveri MM, Tzilos G, Afshar M, Rouse ED, Tian H, Renshaw PF, Ciraulo DA, Yurgelun-Todd DA. Performance on the Stroop predicts treatment compliance in cocaine-dependent individuals. *Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology*. 2008; 33(4):827–836. [PubMed: 17568399]
3. Aharonovich E, Amrhein PC, Bisaga A, Nunes EV, Hasin DS. Cognition, commitment language, and behavioral change among cocaine-dependent patients. *Psychology of addictive behaviors: journal of the Society of Psychologists in Addictive Behaviors*. 2008; 22(4):557–562. [PubMed: 19071981]
4. Aharonovich E, Hasin DS, Brooks AC, Liu X, Bisaga A, Nunes EV. Cognitive deficits predict low treatment retention in cocaine dependent patients. *Drug and alcohol dependence*. 2006; 81(3):313–322. [PubMed: 16171953]
5. Brewer JA, Worhunsky PD, Carroll KM, Rounsaville BJ, Potenza MN. Pretreatment brain activation during stroop task is associated with outcomes in cocaine-dependent patients. *Biological psychiatry*. 2008; 64(11):998–1004. [PubMed: 18635157]
6. Worhunsky PD, Stevens MC, Carroll KM, Rounsaville BJ, Calhoun VD, Pearlson GD, Potenza MN. Functional Brain Networks Associated With Cognitive Control, Cocaine Dependence, and Treatment Outcome. *Psychology of addictive behaviors: journal of the Society of Psychologists in Addictive Behaviors*. In Press.
7. DeVito EE, Worhunsky PD, Carroll KM, Rounsaville BJ, Kober H, Potenza MN. A preliminary study of the neural effects of behavioral therapy for substance use disorders. *Drug and alcohol dependence*. 2012; 122(3):228–235. [PubMed: 22041256]
8. McKeown MJ, Makeig S, Brown GG, Jung TP, Kindermann SS, Bell AJ, Sejnowski TJ. Analysis of fMRI data by blind separation into independent spatial components. *Human brain mapping*. 1998; 6(3):160–188. [PubMed: 9673671]
9. McKeown MJ, Hansen LK, Sejnowski TJ. Independent component analysis of functional MRI: what is signal and what is noise? *Current opinion in neurobiology*. 2003; 13(5):620–629. [PubMed: 14630228]
10. Calhoun VD, Adali T. Unmixing fMRI with independent component analysis. *IEEE engineering in medicine and biology magazine : the quarterly magazine of the Engineering in Medicine & Biology Society*. 2006; 25(2):79–90. [PubMed: 16568940]
11. Calhoun VD, Liu J, Adali T. A review of group ICA for fMRI data and ICA for joint inference of imaging, genetic, and ERP data. *NeuroImage*. 2009; 45(1 Suppl):S163–S172. [PubMed: 19059344]
12. Lee L, Harrison LM, Mechelli A. A report of the functional connectivity workshop, Dusseldorf 2002. *NeuroImage*. 2003; 19(2 Pt 1):457–465. [PubMed: 12814594]
13. Stone JV, Kotter R. Making connections about brain connectivity. *Trends in cognitive sciences*. 2002; 6(8):327–328. [PubMed: 12140078]
14. Friston KJ, Harrison L, Penny W. Dynamic causal modelling. *NeuroImage*. 2003; 19(4):1273–1302. [PubMed: 12948688]
15. Goebel R, Roebroeck A, Kim DS, Formisano E. Investigating directed cortical interactions in time-resolved fMRI data using vector autoregressive modeling and Granger causality mapping. *Magnetic resonance imaging*. 2003; 21(10):1251–1261. [PubMed: 14725933]
16. Harrison L, Penny WD, Friston K. Multivariate autoregressive modeling of fMRI time series. *NeuroImage*. 2003; 19(4):1477–1491. [PubMed: 12948704]
17. Stephan KE, Roebroeck A. A short history of causal modeling of fMRI data. *NeuroImage*. 2012; 62(2):856–863. [PubMed: 22248576]
18. Scheinost D, Benjamin J, Lacadie CM, Vohr B, Schneider KC, Ment LR, Papademetris X, Constable RT. The intrinsic connectivity distribution: a novel contrast measure reflecting voxel level functional connectivity. *NeuroImage*. 2012; 62(3):1510–1519. [PubMed: 22659477]
19. Beveridge TJ, Gill KE, Hanlon CA, Porrino LJ. Review. Parallel studies of cocaine-related neural and cognitive impairment in humans and monkeys. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences*. 2008; 363(1507):3257–3266.

20. Potenza MN, Leung HC, Blumberg HP, Peterson BS, Fulbright RK, Lacadie CM, Skudlarski P, Gore JC. An fMRI Stroop task study of ventromedial prefrontal cortical function in pathological gamblers. *The American journal of psychiatry*. 2003; 160(11):1990–1994. [PubMed: 14594746]
21. First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JB. Structured Clinical Interview for DSM-IV Axis I Disorders--Patient Edition. New York: Biometrics Research Department, New York State Psychiatry Institution; 1996.
22. First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Structured Clinical Interview for DSM-IV-TR Axis I Disorders -- Non-patient Edition (SCID-I/P, 1/2007 revision). New York: Biometrics Research Department, New York State Psychiatric Institute; 2007.
23. Carroll KM, Ball SA, Martino S, Nich C, Babuscio TA, Nuro KF, Gordon MA, Portnoy GA, Rounsaville BJ. Computer-assisted delivery of cognitive-behavioral therapy for addiction: a randomized trial of CBT4CBT. *The American journal of psychiatry*. 2008; 165(7):881–888. [PubMed: 18450927]
24. Balodis IM, Molina ND, Kober H, Worhunsky PD, White MA, Rajita S, Grilo CM, Potenza MN. Divergent neural substrates of inhibitory control in binge eating disorder relative to other manifestations of obesity. *Obesity*. 2013; 21(2):367–377. [PubMed: 23404820]
25. Carroll KM, Kiluk BD, Nich C, DeVito EE, Decker S, LaPaglia D, Duffey D, Babuscio TA, Ball SA. Towards empirical identification of a reliable and clinically meaningful indicator of treatment outcome for drug addiction, Part 1: Features of candidate indicators. Submitted.
26. Nich C, Kiluk BD, Ball SA, LaPaglia D, Duffey D, DeVito EE, Decker S, Babuscio TA, Carroll KM. Towards identification of a reliable and clinically meaningful indicator of treatment outcome for drug addiction, Part 2: Empirical evaluation of cocaine outcome indicators. Submitted.
27. Sobell, LC.; Sobell, MB. Timeline followback: A technique for assessing self-reported alcohol consumption. In: Litten, RZ.; Allen, J., editors. *Measuring alcohol consumption: Psychosocial and biological methods*. New Jersey: Humana Press; 1992. p. 41-72.
28. Higgins ST, Wong CJ, Badger GJ, Ogden DE, Dantona RL. Contingent reinforcement increases cocaine abstinence during outpatient treatment and 1 year of follow-up. *Journal of consulting and clinical psychology*. 2000; 68(1):64–72. [PubMed: 10710841]
29. Peterson BS, Kane MJ, Alexander GM, Lacadie C, Skudlarski P, Leung HC, May J, Gore JC. An event-related functional MRI study comparing interference effects in the Simon and Stroop tasks. *Brain research. Cognitive brain research*. 2002; 13(3):427–440. [PubMed: 11919006]
30. Joshi A, Scheinost D, Okuda H, Belhachemi D, Murphy I, Staib LH, Papademetris X. Unified framework for development, deployment and robust testing of neuroimaging algorithms. *Neuroinformatics*. 2011; 9(1):69–84. [PubMed: 21249532]
31. Cole MW, Pathak S, Schneider W. Identifying the brain's most globally connected regions. *NeuroImage*. 2010; 49(4):3132–3148. [PubMed: 19909818]
32. Buckner RL, Sepulcre J, Talukdar T, Krienen FM, Liu H, Hedden T, Andrews-Hanna JR, Sperling RA, Johnson KA. Cortical hubs revealed by intrinsic functional connectivity: mapping, assessment of stability, and relation to Alzheimer's disease. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2009; 29(6):1860–1873. [PubMed: 19211893]
33. Van Dijk KR, Sabuncu MR, Buckner RL. The influence of head motion on intrinsic functional connectivity MRI. *Neuroimage*. 2012; 59(1):431–438. [PubMed: 21810475]
34. Narayanan A, White CA, Saklayen SS, Abduljalil A, Schmalbrock P, Pepper TH, Lander BN, Beversdorf DQ. Functional connectivity during language processing in acute cocaine withdrawal: a pilot study. *Neurocase*. 2012; 18(6):441–449. [PubMed: 22082460]
35. Verdejo-Garcia A, Contreras-Rodriguez O, Fonseca F, Cuenca A, Soriano-Mas C, Rodriguez J, Pardo-Lozano R, Blanco-Hinojo L, de Sola Llopis S, Farre M, Torrens M, Pujol J, de la Torre R. Functional alteration in frontolimbic systems relevant to moral judgment in cocaine-dependent subjects. *Addiction biology*. 2012
36. Tomasi D, Volkow ND, Wang R, Carrillo JH, Maloney T, Alia-Klein N, Woicik PA, Telang F, Goldstein RZ. Disrupted functional connectivity with dopaminergic midbrain in cocaine abusers. *PLoS One*. 2010; 5(5):e10815. [PubMed: 20520835]

37. Gu H, Salmeron BJ, Ross TJ, Geng X, Zhan W, Stein EA, Yang Y. Mesocorticolimbic circuits are impaired in chronic cocaine users as demonstrated by resting-state functional connectivity. *NeuroImage*. 2010; 53(2):593–601. [PubMed: 20603217]
38. Kelly C, Zuo XN, Gotimer K, Cox CL, Lynch L, Brock D, Imperati D, Garavan H, Rotrosen J, Castellanos FX, Milham MP. Reduced interhemispheric resting state functional connectivity in cocaine addiction. *Biological psychiatry*. 2011; 69(7):684–692. [PubMed: 21251646]
39. Li SJ, Biswal B, Li Z, Risinger R, Rainey C, Cho JK, Salmeron BJ, Stein EA. Cocaine administration decreases functional connectivity in human primary visual and motor cortex as detected by functional MRI. *Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine*. 2000; 43(1):45–51. [PubMed: 10642730]
40. Tops M, Boksem MA. A potential role of the inferior frontal gyrus and anterior insula in cognitive control, brain rhythms, and event-related potentials. *Frontiers in psychology*. 2011; 2:330. [PubMed: 22084637]
41. Bunge SA, Dudukovic NM, Thomason ME, Vaidya CJ, Gabrieli JD. Immature frontal lobe contributions to cognitive control in children: evidence from fMRI. *Neuron*. 2002; 33(2):301–311. [PubMed: 11804576]
42. Garavan H, Ross TJ, Murphy K, Roche RA, Stein EA. Dissociable executive functions in the dynamic control of behavior: inhibition, error detection, and correction. *NeuroImage*. 2002; 17(4):1820–1829. [PubMed: 12498755]
43. Konishi S, Nakajima K, Uchida I, Kikyo H, Kameyama M, Miyashita Y. Common inhibitory mechanism in human inferior prefrontal cortex revealed by event-related functional MRI. *Brain : a journal of neurology*. 1999; 122(Pt 5):981–991. [PubMed: 10355680]
44. Konishi S, Nakajima K, Uchida I, Sekihara K, Miyashita Y. No-go dominant brain activity in human inferior prefrontal cortex revealed by functional magnetic resonance imaging. *The European journal of neuroscience*. 1998; 10(3):1209–1213. [PubMed: 9753190]
45. Menon V, Adelman NE, White CD, Glover GH, Reiss AL. Error-related brain activation during a Go/NoGo response inhibition task. *Human brain mapping*. 2001; 12(3):131–143. [PubMed: 11170305]
46. Iversen SD, Mishkin M. Perseverative interference in monkeys following selective lesions of the inferior prefrontal convexity. *Experimental brain research. Experimentelle Hirnforschung. Experimentation cerebrale*. 1970; 11(4):376–386.
47. Aron AR, Monsell S, Sahakian BJ, Robbins TW. A componential analysis of task-switching deficits associated with lesions of left and right frontal cortex. *Brain : a journal of neurology*. 2004; 127(Pt 7):1561–1573. [PubMed: 15090477]
48. Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, Reiss AL, Greicius MD. Dissociable intrinsic connectivity networks for salience processing and executive control. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2007; 27(9):2349–2356. [PubMed: 17329432]
49. Robinson TE, Berridge KC. Addiction. *Annual review of psychology*. 2003; 54:25–53.
50. Aron AR, Shohamy D, Clark J, Myers C, Gluck MA, Poldrack RA. Human midbrain sensitivity to cognitive feedback and uncertainty during classification learning. *Journal of neurophysiology*. 2004; 92(2):1144–1152. [PubMed: 15014103]
51. Rodriguez PF, Aron AR, Poldrack RA. Ventral-striatal/nucleus-accumbens sensitivity to prediction errors during classification learning. *Human brain mapping*. 2006; 27(4):306–313. [PubMed: 16092133]
52. Schultz W. Behavioral theories and the neurophysiology of reward. *Annual review of psychology*. 2006; 57:87–115.
53. Shohamy D, Myers CE, Kalanithi J, Gluck MA. Basal ganglia and dopamine contributions to probabilistic category learning. *Neuroscience and biobehavioral reviews*. 2008; 32(2):219–236. [PubMed: 18061261]
54. Murdaugh DL, Cox JE, Cook EW 3rd, Weller RE. fMRI reactivity to high-calorie food pictures predicts short- and long-term outcome in a weight-loss program. *NeuroImage*. 2012; 59(3):2709–2721. [PubMed: 22332246]

55. Paulus MP, Tapert SF, Schulteis G. The role of interoception and alliesthesia in addiction. *Pharmacology, biochemistry, and behavior*. 2009; 94(1):1–7.
56. Janes AC, Pizzagalli DA, Richardt S, de BFB, Chuzi S, Pachas G, Culhane MA, Holmes AJ, Fava M, Evins AE, Kaufman MJ. Brain reactivity to smoking cues prior to smoking cessation predicts ability to maintain tobacco abstinence. *Biological psychiatry*. 2010; 67(8):722–729. [PubMed: 20172508]
57. Naqvi NH, Rudrauf D, Damasio H, Bechara A. Damage to the insula disrupts addiction to cigarette smoking. *Science*. 2007; 315(5811):531–534. [PubMed: 17255515]
58. Tanabe J, Tregellas JR, Dalwani M, Thompson L, Owens E, Crowley T, Banich M. Medial orbitofrontal cortex gray matter is reduced in abstinent substance-dependent individuals. *Biological psychiatry*. 2009; 65(2):160–164. [PubMed: 18801475]
59. Potenza MN, Sofuoglu M, Carroll KM, Rounsaville BJ. Neuroscience of behavioral and pharmacological treatments for addictions. *Neuron*. 2011; 69(4):695–712. [PubMed: 21338880]
60. Easton C, Bauer LO. Neuropsychological differences between alcohol-dependent and cocaine-dependent patients with or without problematic drinking. *Psychiatry research*. 1997; 71(2):97–103. [PubMed: 9255854]
61. Fox HC, Bergquist KL, Casey J, Hong KA, Sinha R. Selective cocaine-related difficulties in emotional intelligence: relationship to stress and impulse control. *The American journal on addictions / American Academy of Psychiatrists in Alcoholism and Addictions*. 2011; 20(2):151–160. [PubMed: 21314758]
62. Ollo C, Lindquist T, Alim TN, Deutsch SI. Predicting premorbid functioning in crack-cocaine abusers. *Drug and alcohol dependence*. 1995; 40(2):173–175. [PubMed: 8745140]
63. Easton C, Bauer LO. Neuropsychological correlates of urine toxicology results. *Progress in neuro-psychopharmacology & biological psychiatry*. 1996; 20(6):969–982. [PubMed: 8888104]

Cocaine-Dependent vs. Healthy Comparison Overall Intrinsic Connectivity during fMRI Stroop

Figure 1. Cocaine Dependent versus Comparison Group Overall Intrinsic Connectivity during fMRI Stroop

Axial view depicting whole-brain analysis of intrinsic connectivity. Maps are thresholded at a voxel-level threshold of $p < 0.05$ with a conjoint cluster threshold corresponding to a $p < 0.05$ family-wise error (FWE) correction. Blue color depicts less non-mean-adjusted intrinsic connectivity in the cocaine-dependent group relative to healthy comparison subjects. There were no regions where the cocaine-dependent group (n=15) showed greater non-mean-adjusted intrinsic connectivity than did the healthy comparison group (n=15). The right side of the brain is on the left.

Cocaine-Dependent vs. Healthy Comparison Mean-Adjusted Intrinsic Connectivity during fMRI Stroop

Figure 2. Cocaine Dependent versus Comparison Group Mean-Adjusted Intrinsic Connectivity during fMRI Stroop

Axial view depicting whole-brain analysis of intrinsic connectivity mean-adjusted for individual degree of overall intrinsic connectivity. Maps are thresholded at a voxel-level threshold of $p < 0.05$ with a conjoint cluster threshold corresponding to a $p < 0.05$ family-wise error (FWE) correction. Red/orange color indicates greater mean-adjusted intrinsic connectivity in the cocaine-dependent ($n=15$) relative to the healthy comparison group. There were no regions where the healthy comparison group showed greater mean-adjusted intrinsic connectivity than the cocaine-dependent group ($n=15$). The right side of the brain is on the left.

Intrinsic Connectivity during fMRI Stroop is Associated with Measures of Treatment Outcome

Figure 3. Intrinsic Connectivity during fMRI Stroop is Associated with Measures of Treatment Outcome

Axial view depicting whole brain analysis of non-mean-adjusted intrinsic connectivity correlations between fMRI Stroop and: a) the maximum days of self-reported primary drug abstinence during treatment; and, b) percent of positive urine screens during treatment. Analyses are restricted to the cocaine-dependent group with available treatment outcome data ($n=11$). Maps are thresholded at a voxel-level threshold of $p<0.05$ with a conjoint cluster threshold corresponding to a $p<0.05$ family-wise error (FWE) correction. Red/orange color indicates positive correlations between measures; blue/purple color depicts negative correlations between measures. The right side of the brain is on the left.

Table 1

Characteristic	Cocaine-Dependent (N=15)		Healthy Comparison (N=15)	
	N	%	N	%
<u>Demographics</u>				
Total N (N female)	15 (9)		15 (8)	
Race				
Caucasian	6	40.0	8	53.3
African American	10	66.7	7	46.7
Asian	0	0.0	0	0.0
Highest Education Level				
No High School	1	6.7	0	0.0
Partial High School	1	6.7	0	0.0
High School Completed	9	60.0	3	20.0
Partial College	4	26.7	3	20.0
College Completed	1	6.7	10	66.7
<u>Baseline Clinical and Substance Use Measures</u>				
Psychiatric Diagnosis				
Lifetime Major Depression	6	40.0		
Antisocial Personality Disorder	3	20.0		
Lifetime Substance-Induced Mood Disorder	2	13.3		
Current Substance-Induced Mood Disorder	1	6.7		
Lifetime Alcohol Use Disorder	6	40.0		
Current Alcohol Disorder	1	6.7		
Lifetime Cannabis Disorder	12	80.0		
Current Cannabis Disorder	0	0.0		
Daily Cigarette Smoker				
Days Use in 28 Days Prior to Treatment				
Cocaine	14	93.3		
Heroin	3	20.0		
Alcohol	7	46.7		
Cannabis	3	20.0		
Cigarette	15	100.0		
Lifetime Years of Substance Use				
Cocaine	14	93.3		
Heroin	7	46.7		
Alcohol	6	40.0		
Cannabis	12	80.0		
Cigarette	N/A			
	Mean	SD	Mean	SD
<u>Demographics</u>				
Age (Years)	39.0	10.4	40.00	7.4
	86.07	14.6		

Characteristic	Cocaine-Dependent (N=15)		Healthy Comparison (N=15)	
	N	%	N	%
Estimated IQ (Shipley Institute of Living Scale)			106.31	9.68
<u>Baseline Clinical and Substance Use Measures</u>				
Days Use in 28 Days Prior to Treatment				
Cocaine	14.33	10.5		
Heroin	0.33	0.82		
Alcohol	3.40	5.24		
Cannabis	1.47	3.907		
Cigarette	27.07	3.62		
Lifetime Years of Substance Use				
Cocaine	11.06	7.91		
Heroin	5.87	11.20		
Alcohol	10.60	10.72		
Cannabis	7.20	7.93		
Cigarette	N/A	N/A		
<u>Treatment Engagement and Outcome</u>				
Days in Treatment	47.77	24.62		
Percent Negative Urines	41.89	45.95		
Maximum Self-Reported Consecutive Days				
Abstinence	27.08	24.11		
<u>Stroop Behavioral Measures^a</u>	Mean	SD	Mean	SD
Congruent Trial Response Time (ms)	579.74	85	592	110.96
Incongruent Trial Response Time (ms)	807.60	173	813	170.98
Number of Errors During Incongruent Trials	5.73	5.98	5.08	5.3

Table 2
Between-group Differences (Cocaine-Dependent versus Healthy Comparison) in Intrinsic Connectivity during Stroop Task

Cluster Subregion	L/R	X	Y	Z	Volume (mm ³)	Volume (voxel)	Mean t-value
ACC, PCC, Cingulate Gyrus, IFG, Insula, Thalamus, Amygdala, Visual Cortex, Brainstem		-2	-26	7	403346	14938.74	-2533.21
Insula	R	39	7	0	5498	203.63	-2399.63
Insula	L	-39	-5	2	6307	233.59	-2444.2
Amygdala	R	19	-4	-15	1491	55.22	-2534.11
Amygdala	L	-23	-5	-15	1144	42.37	-2378.84
Thalamus	R	7	-14	9	2402	88.96	-2627.13
Thalamus	L	-8	-15	10	2221	82.26	-2525.92
Hippocampus	R	27	-25	-6	671	24.85	-2279.75
Hippocampus	L	-28	-26	-6	1564	57.93	-2437.82
Caudate	R	12	11	6	1014	37.56	-2335.26
Caudate	L	-11	15	1	586	21.70	-2506.16

Data represent regions where the cocaine-dependent group (n=15) demonstrated diminished Stroop-effect-related intrinsic connectivity relative to the comparison group (n=15). Coordinates are Talairach (x, y, z) and are reported as the center of mass of the cluster. L = left, R = right, IFG = inferior frontal gyrus, ACC = anterior cingulate cortex, PCC = posterior cingulate cortex.

Table 3

Between-group Differences (Cocaine-Dependent versus Healthy Comparison) in Mean-Adjusted Intrinsic Connectivity during Stroop Task

Cluster Subregion	L/R	X	Y	Z	Volume (mm ³)	Volume (voxel)	Mean t-value
OFC, Putamen, Insula, IFG	R	-23	18	2	7776	228	2605.68
OFC	R	21	32	-14	3044	112.74	2440.65
Putamen	R	25	7	1	2502	92.67	2669.67
IFG	R	31	20	13	607	22.48	2632.17
Insula	R	29	20	2	229	8.48	2385.27
OFC, Putamen, Caudate, Insula, IFG	L	25	20	-4	7809	289.22	2523.88
Putamen	L	-23	10	4	924	34.22	2635.34
OFC	L	-13	25	-17	2194	81.26	2396.94
Caudate	L	-16	16	13	241	8.93	2541.31
Insula	L	-30	14	10	1411	52.26	2848.33
IFG	L	-34	16	12	1771	65.59	2678.09
Cingulate Gyrus	L	22	10	43	9156	339.11	2574.88

Data represent regions where the cocaine-dependent group (n=15) demonstrated greater Stroop-effect-related intrinsic connectivity relative to the healthy comparison group (n=15), after data were adjusted to each subject's mean connectivity. Coordinates are Talairach (x, y, z) and are reported as the center of mass of the cluster. L = left, R = right, IFG = inferior frontal gyrus, OFC = orbitofrontal cortex.

Table 4

A Negative Correlations between Non-Mean-Adjusted Intrinsic Connectivity during Stroop Task and Maximum Consecutive Days of Cocaine Abstinence During Treatment

Cluster Subregion	L/R	X	Y	Z	Volume (mm ³)	Volume (voxel)	Mean r-value
Brainstem, Thalamus, Ventral Striatum, Substantia Nigra		2	-18	2	13376	495.41	-0.64
Thalamus	R	8	-24	8	1341	49.67	-0.64
Thalamus	L	-6	-18	7	2889	107	-0.64
Ventral Striatum	R	6	0	-3	636	23.56	-0.61
Ventral Striatum	L	-16	3	-5	191	7.07	-0.59
Substantia Nigra	R	13	-18	-7	251	9.30	-0.65
Substantia Nigra	L	-11	-20	-7	284	10.52	-0.64

B Positive Correlations between Non-Mean-Adjusted Intrinsic Connectivity during Stroop Task and Percent Positive Urine Screens During Treatment

Cluster Subregion	L/R	X	Y	Z	Volume (mm ³)	Volume (voxel)	Mean r-value
Cerebellum	R	22	-71	-17	4872	184.15	0.64
Thalamus, Ventral Striatum, Brainstem, Insula, Hippocampus		0	-13	-2	16258	602.15	0.64
Thalamus	R	7	-22	6	1595	59.07	0.66
Thalamus	L	-6	-21	6	2542	94.15	0.67
Ventral Striatum	R	17	0	-5	1326	49.11	0.63
Ventral Striatum	L	-17	0	-5	1344	49.78	0.61
Substantia Nigra	R	14	-20	-8	335	12.41	0.67
Substantia Nigra	L	-8	-18	-8	217	8.04	0.64
Insula	R	36	-5	-2	588	21.78	0.63
Hippocampus	L	-31	-14	-11	765	28.33	0.63

Data represent regions where Stroop-effect-related non-mean-adjusted intrinsic connectivity within the cocaine-dependent group (n=13) correlated negatively with longest duration of cocaine abstinence during treatment. Coordinates are Talairach (x, y, z) and are reported as the center of mass of the cluster. L = left, R = right.

Data represent regions where Stroop-effect-related non-mean-adjusted intrinsic connectivity within the cocaine-dependent group (n=13) correlated positively with percent of urine toxicology tests positive for cocaine use during treatment. Coordinates are Talairach (x, y, z) and are reported as the center of mass of the cluster. L = left, R = right.