Pretreatment Brain Activation During Stroop Task Is Associated with Outcomes in Cocaine-Dependent Patients

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Background: Cognitive behavioral and related therapies for cocaine dependence may exert their effects, in part, by enhancing cognitive control over drug use behavior. No prior studies have systematically examined the neural correlates of cognitive control as related to treatment outcomes for cocaine dependence.

Methods: Twenty treatment-seeking cocaine-dependent individuals performed a Stroop color-word interference task while undergoing functional magnetic resonance imaging (fMRI) prior to initiating treatment. The primary outcome measures were percent of urine drug screens negative for cocaine, percent days abstinent, and treatment retention. Correlations between regional brain activation during Stroop task performance and treatment outcome measures were analyzed.

Results: During Stroop performance, individuals activated brain regions similar to those reported in nonaddicted individuals, including the anterior cingulate cortex, dorsolateral prefrontal cortex, parietal lobule, insula, and striatum. Activations at treatment onset correlated differentially with specific outcomes: longer duration of self-reported abstinence correlated with activation of ventromedial prefrontal cortex, left posterior cingulate cortex, and right striatum; percent drug-free urine screens correlated with striatal activation; and treatment retention correlated with diminished activation of dorsolateral prefrontal cortex. A modest correlation between Stroop effect and treatment retention was found.

Conclusions: The functions of specific brain regions underlying cognitive control relate differentially to discrete outcomes for the treatment of cocaine dependence. These findings implicate neurocircuitry underlying cognitive control in behavioral treatment outcome and provide insight into the mechanisms of behavioral therapies for cocaine dependence. They also suggest neural activation patterns during cognitive control tasks are more sensitive predictors of treatment response than behavioral measures.

Key Words: Addiction, cocaine, cognitive behavioral therapy, cognitive control, fMRI, Stroop, treatment outcomes

There are over 40 million Americans reporting lifetime use of cocaine or crack (1). Behavioral therapies remain the mainstay of treatment for cocaine dependence, as there are no Food and Drug Administration (FDA)-approved pharmacotherapies (2). Predictors of treatment outcomes, ranging from demographics to biological markers, have yielded mixed results (3). Neurobiological features of cocaine dependence may help identify patients who can best utilize treatments. Compared with self-reported measures, brain activity may be able to better predict outcomes, possibly by bypassing conscious or subconscious processes (e.g., embarrassment, deceit, or denial).

Cognitive control has been defined as the series of processes by which the human cognitive system is able to configure itself for the performance of specific tasks through appropriate adjustments in perceptual selection, response biasing, and the online maintenance of contextual information (4). Prefrontal networks involving the dorsolateral prefrontal cortex (dlPFC), orbitofrontal cortex (OFC), and anterior cingulate cortex (ACC) are important for executive cognitive functions governing cognitive control such as response inhibition and error monitoring (5). Dysregulation in these networks may mediate core characteristics of drug addiction (6), as cocaine abusers have shown dysfunction in tasks of decision making and cognitive control (7), which correlates with abnormalities in these networks (8).

The objective of this study was to evaluate relationships between pretreatment regional brain activations during a cognitive control task and treatment outcomes in cocaine-dependent individuals undergoing behavioral therapy. We chose the Stroop color-word interference task because it is a well-validated cognitive control task and has been used with cocaine-dependent populations previously (8,9). Treatment outcome measures were percent of urine toxicology screens positive for cocaine, self-reported abstinence, and treatment retention. We hypothesized that neurocircuitry activation underlying cognitive control would correlate with treatment retention and drug abstinence. We also hypothesized that Stroop performance would correlate with treatment outcome, albeit less robustly.

Methods and Materials

Participants

All participants in two randomized clinical trials for treatment-seeking, cocaine-dependent individuals were offered participation in this study prior to beginning treatment. Twenty-two subjects agreed. Two were excluded for excessive motion during functional magnetic resonance imaging (fMRI) tasks. Study 1 (n = 8) compared a computer-assisted version of cognitive behavioral therapy (CBT) with a standard community-based drug treatment program as described elsewhere (10). Participants received either weekly individual plus group sessions (treatment as usual [TAU]) or TAU plus a multimedia computer-assisted version of CBT to which patients had access twice weekly during 8 weeks of treatment. Participants received urine screens twice weekly. Study 2 (n = 12) was a randomized clinical trial of

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cocaine users randomized to individual CBT in conjunction with one of four conditions: 1) placebo, 2) disulfiram, 3) contingency management + placebo, or 4) contingency management + disulfiram. Contingency management consisted of providing positive reinforcement for cocaine-free urines. Participants received CBT once weekly plus medications and urine screens thrice weekly.

Participants were English-speaking adults who met current DSM-IV criteria for cocaine dependence via structured clinical interviews (Structured Clinical Interview for DSM-IV [SCID]). Participants were excluded if they had not used cocaine within the past 28 days, were pregnant or breastfeeding, color blind, left-handed, had less than a third grade reading level, could not commit to completing 8 weeks of treatment, had an untreated psychotic disorder that precluded outpatient treatment, had a psychiatric disorder with current use of a prescribed psychotropic medication that could not be discontinued (study 2 only), or had any acute or unstable medical or neurological illness.

Participants in both studies were similar with regard to age, sex, race, education level, drug use history, employment status, and Axis I comorbidity; blood oxygenation level-dependent (BOLD) signal changes; medication effects; treatment outcome correlations; and Stroop reaction time (RT) (all $p > .2$, Table 1) and were thus included in a single group for analyses as has been done previously (9).

Participants reported last use of cocaine an average (±SD) of 5.35 (±5.68) days (30%, 45%, and 80% reporting use within 1, 3, and 7 days, respectively) before imaging. Sixty-five percent reported any use of alcohol in the month prior to treatment. Of these, participants reported their last use averaging 13.92 (±10.29) days (5%, 5%, and 25% reporting use within 1, 3, and 7 days, respectively) prior to imaging. Zero and 5% reported marijuana use within 1 and 3 days before imaging, respectively, and 5% reported benzodiazepine use (as prescribed) the day before imaging. Participants showed no signs of intoxication or withdrawal from any drugs during imaging sessions.

Table 1. Demographic and Clinical Characteristics ($n = 20$)

Demographics		%
Age: years (SD)	38.60 (9.29)	
Gender, female	8	40
Race		
White	6	30
Black	10	50
Hispanic	4	20
Ethnicity		
Hispanic	4	20
Non-Hispanic	16	80
Employment status		
Full-time	1	5
Part-time	4	20
Unemployed/Not working	15	75
Education: years (SD)	12.70 (1.17)	
Shipley Scale IQ score: mean IQ (SD)	90.35 (12.77)	
Clinical Characteristics		
Cocaine use prior to treatment: days out of 28 (SD)	12.30 (9.49)	
Lifetime cocaine use: years (SD)	11.05 (7.86)	
Daily tobacco smoker	17	85
Comorbid Diagnosis		
Current Depressive Disorder	0	0
Lifetime Depressive Disorder	10	50
Anti-social Personality Disorder	4	20
Lifetime Alcohol Dependence/Abuse	11	55
Current Alcohol Dependence/Abuse	4	20
Lifetime Marijuana Dependence/Abuse	12	60
Current Marijuana Dependence/Abuse	2	10
Lifetime Opioid Dependence/Abuse	4	20
Current Opioid Dependence/Abuse	3	15
Treatment Conditions		
Study 1		
CBT + TAU	5	25
TAU	3	15
Study 2		
CBT + Placebo	4	20
CBT + Disulfiram	4	20
CBT + Placebo + CM	3	15
CBT + Disulfiram + CM	1	5

CBT, cognitive behavioral therapy; CM, contingency management; TAU, treatment as usual.

fMRI Task

The event-related fMRI Stroop color-word interference task has been described previously (11–15). Briefly, subjects completed 6 runs of 105 stimuli during the fMRI acquisition. Each stimulus was presented for 1300 msec with an intertrial interval of 350 msec. Incongruent stimuli were presented pseudorandomly every 13 to 16 congruent stimuli, with a total of 7 incongruent events in each run (which has been shown to produce a Stroop rather than an "oddball" effect) (14). Participants completed a maximum of 5 (4.58 ± 1.21) additional runs to assess Stroop effect (difference in RT to incongruent versus congruent stimuli) (16,17) and percentage of correct responses to incongruent stimuli.

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 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 (repetition time/echo time [TR/TE] 1500/27 msec, flip angle 60°, field of view [FOV] 22 cm × 22 cm, 64 × 64 matrix, 3.4 mm × 3.4 mm in-plane resolution, 5 mm effective slice thickness, 25 slices). Each stimulus run consisted of 124 volumes, including an initial rest period of 9 seconds that was removed from analyses.

fMRI Data Analysis

Functional images were analyzed using SPM2 (Wellcome Functional Imaging Laboratory, London, United Kingdom). Each run was separately realigned using INRIAlign (Wellcome Functional Imaging Laboratory) (18) and was examined for head motion in excess of one voxel. Single runs were removed from 3 of the 20 subjects for excessive motion. Realigned image volumes for each session were used to construct a mean functional image volume, which was then used for spatial normalization into Montreal Neurological Institute (MNI) standardized space. The normalization parameters for each participant were then applied to the corresponding functional image volumes using an automated spatial transformation resulting in an isometric voxel size of $4 \times 4 \times 4$ mm^3. Normalized images were then smoothed with a 9 mm full-width at half-maximum Gaussian filter.

Data were analyzed using the general linear model approach. Analysis was performed by modeling congruent and incongruent stimuli separately in an event-related design using the hemody-

namic response function with time derivative provided by SPM2. A high-pass filter (cutoff period = 128 sec) was used to remove low-frequency signals and the SPM2 first-order autoregressive (AR[1]) process was used to correct for serial correlations. Resulting images representing the estimated hemodynamic response amplitude (positive and negative) for each condition were then reestimated with a latency variation amplitude-correction method (19). The latency-corrected contrast images were then used in random-effects and correlational group analyses.

Main effects were examined in a one-sample *t* test at a significance level of $p < .00005$ uncorrected and a cluster threshold of $k > 20$. Correlations between the activation contrasts for the Stroop task and treatment outcome variables were assessed using SPM2 simple regression analysis and a significance level of $p < .005$ uncorrected and a cluster threshold of $k > 20$. If no significant correlations were found at $p < .005$, the significance threshold was relaxed to $p < .01$. Covariants were analyzed using SPM2 multiple regression models. Significant clusters (main effect activation and outcome correlations) were used to define regions of interest. Average percent signal change within each region was calculated using the latency-corrected contrast image for each subject.

Results

Behavioral Results–Stroop Task Performance

Reaction time to congruent stimuli correlated with RT to incongruent stimuli and Stroop effect (Table 2). Stroop effect inversely correlated with RT to incongruent stimuli and percent incorrect responses, perhaps because the Stroop effect is calculated from RTs. Percent cocaine-free urine toxicology correlated with self-reported longest abstinence. Reaction times to congruent and incongruent stimuli and Stroop effect correlated moderately with number of weeks in treatment. No other correlations between Stroop performance, urine toxicology, reported abstinence, and treatment retention were found. Participants performing the Stroop task had an average (±SD) incorrect response percentage of 27.0% (±24.9%) to incongruent stimuli.

Imaging Results–Brain Activation During Stroop Performance

During Stroop performance, subjects showed significantly greater BOLD signal in the contrast of incongruent versus congruent conditions. Regional activations predominantly involved the 1) dorsal ACC extending dorsally and anteriorally into the medial and superior frontal gyri; 2) putamen/globus pallidus; 3) dlPFC including the inferior and middle frontal gyri, extending posteriorally to the precentral gyri and ventrally into the insula and superior temporal gyri; and 4) superior parietal lobule extending into the inferior parietal lobule bilaterally (Supplement 1, Table 3A).

Clinical Correlations–Brain Activation Correlates with Treatment Outcome Measures

Brain activations during Stroop performance correlated differentially with treatment outcome measures. Percent cocaine negative urine toxicology correlated with activations centered in the right putamen (Figure 1A, Table 3B). Self-reported longest duration of cocaine abstinence correlated with activation of the 1) right putamen; 2) left ventromedial prefrontal cortex (vmPFC), involving the medial frontal gyrus/OFC and ventral portion of the superior frontal gyrus, extending dorsally into the ventral ACC; and 3) left posterior cingulate cortex (PCC) extending into the superior parietal lobule (Figure 1B and 1C, Table 3C). Inverse correlations between activation during the Stroop task and number of weeks in treatment were observed in left dlPFC (Figure 1D, Table 3D).

Clinical Correlations–Brain Activation Correlates Modestly with Stroop Performance

Post hoc region of interest (ROI) analysis (all regions listed in Table 3) revealed a moderate inverse correlation between incongruent and congruent RTs and percent signal change in the left dlPFC associated with retention ($r = -.47, -.46$; $p < .05$). The correlation between this region and Stroop effect, however, did not reach but trended toward significance ($r = -.39, .1$; $p > .05$). No other correlations between RTs, Stroop effect, and brain activation were found in any ROI. No correlations between ROI activation and age, education, gender, last reported cocaine use, or days of cocaine use in the month before treatment were found.

Discussion

This study is one of the first to investigate the relationship between brain activations and treatment outcomes for individuals with cocaine dependence and the first to investigate brain

Table 2. Stroop Task Performance Correlates Minimally with Treatment Outcome Measures

		Pearson Correlation Coefficient (*r*)					
	Mean (SD)	RT Incongruent	Stroop Effect	% Incorrect Responses	% Cocaine Negative Urines	Longest abstinence from Cocaine	Weeks in Treatment
Stroop Performance							
Reaction time, congruent stimuli (msec)	579.5 (75.5)	.87[c]	.62[b]	−.32	.00	−.09	.45[a]
Reaction time, incongruent stimuli (msec)	792.3 (155.0)		.92[c]	−.46[a]	.11	.09	.50[a]
Stroop effect (msec)	212.8 (96.5)			−.50[a]	.18	.23	.46[a]
Percent incorrect incongruent responses	27.0 (24.9)				−.21	−.11	.12
Outcome							
Percent cocaine-negative urines	58.4 (46.8)					.74[c]	.01
Longest abstinence from cocaine (days)	32.0 (21.4)						.03
Weeks in treatment	5.5 (3.1)						

RT, reaction time.
Data are given as mean ± standard deviation.
[a] $p < .05$.
[b] $p < .01$.
[c] $p < .001$.

Table 3. Regional Brain Activation During Stroop Task Performance and Correlations with Treatment Outcome Measures

	BA	Size	Z^a	x	y	z
A. Stroop Main Effect Contrast (Incongruent vs. Congruent)						
peak voxel threshold: $p < .00005$; cluster threshold: k > 20						
R Dorsolateral Prefrontal Cortex/Insula	13, 38, 45, 46, 47	415	6.34	36	28	−8
L Dorsolateral Prefrontal Cortex/Insula	13, 38, 44, 45, 46, 47	539	6.03	−40	8	32
Medial Frontal Cortex/Anterior Cingulate	6, 8, 9, 24, 32	572	5.97	−4	12	52
L Medial Globus Pallidus/Putamen		49	4.95	−16	4	0
R Medial Globus Pallidus/Putamen		67	4.86	12	0	−4
L Parital Lobule	7, 40	51	4.71	−32	−60	44
R Parital Lobule	40	22	4.48	52	−48	48
B. Stroop Main Effect Correlation with Percent Cocaine-Negative Urine Toxicology						
peak voxel threshold: $p < .005$; cluster threshold: k > 20						
R Putamen		45	4.11	24	0	−4
C. Stroop Main Effect Correlation with Longest Duration of Cocaine Abstinence						
peak voxel threshold: $p < .005$; cluster threshold: k > 20						
L Posterior Cingulate Cortex	31	31	3.72	−24	−36	40
L Ventral Medial Prefrontal Cortex	10, 32	24	3.69	−12	48	−8
R Putamen		35	3.20	24	0	12
D. Stroop Main Effect Correlation with Weeks in Treatment						
peak voxel threshold: $p < .01^b$, cluster threshold: k > 20						
L Dorsal Lateral Prefrontal Cortex	8, 9	46	−2.88	−28	40	48

BA, Broadman Area; BOLD, blood oxygenation level-dependent; C, congruent; I, incongruent; L, left; R, right; Size, cluster size.

A. Brain regions showing significant differences with incongruent versus congruent stimuli during Stroop task performance. B. Percent cocaine-negative urine toxicology over the course of treatment. C. Longest duration of self-reported cocaine abstinence. D. Total weeks in treatment.

[a]For A: Z indicates I > C BOLD signal; no C > I BOLD signal was observed. For B–D: $Z > 0$ indicates a positive correlation and $Z < 0$ indicates an inverse correlation.

[b]No significant correlations were found at $p < .005$ and thus the significance threshold was relaxed to $p < .01$.

activations underlying cognitive control in relation to outcome measures for behavioral treatment of cocaine dependence. During Stroop task execution, individuals activated brain regions similar to those reported in nonaddicted individuals on this task (14,20,21). Regional brain activations at treatment onset correlated differentially with outcome measures, supporting our hypothesis that cognitive control neurocircuitry activation would correlate with treatment retention and drug abstinence. Our hypothesis that Stroop performance would correlate with treatment outcome was partially supported, as RTs only correlated with dlPFC activation.

Stroop Performance in Addiction

A study of cocaine-dependent individuals compared Stroop task subscale and Hamilton Depression Rating Scale scores using logistic regression analysis to predict treatment completion (9). They found that treatment completers performed better on color naming and interference on the Stroop task and that models based on Stroop scores predicted dropout more robustly than did those based on depression scores. In accord with these results, we also found a modest correlation between Stroop effect and treatment retention.

fMRI of Stroop in Cocaine Dependence

Activation patterns during the Stroop task were seen in regions previously reported in both substance abusers and control groups (8,14,15,20), thus supporting the validity of the Stroop fMRI paradigm. As the current study did not involve healthy control subjects, future investigations are needed to examine directly for possible between-group differences during Stroop performance.

Cognitive Control and Behavioral Therapy for Cocaine Dependence

Prefrontal cortex regions contribute to cognitive control involving error detection, performance monitoring, and establishing motivational value of rewards (22). Reward prediction error signals correlate with activation of the putamen (23), indicating that corticostriatal brain regions function as a circuit during cognitive control processes. In this circuit, the dorsal striatum "gates" afferent information entering the PFC, allowing for the preservation and updating of goals (24,25). The PCC, which is anatomically linked to the PFC and striatum, has been implicated in sensory arousal (e.g., cocaine cues) (26,27), motivationally linked attention (28), and the evaluation of emotional memories (29). We found that during Stroop task performance, activation in specific corticostriatal regions correlated with reported abstinence and cocaine-free urine toxicology. Increased activity in the putamen may reflect gating of informational processing with concomitant increased PFC and PCC activation signifying attending to, resisting, or reevaluating motivationally salient stimuli, such as cravings and/or emotional memories elicited by stressful situations or drug-related cues, which have been associated with dysfunction in this circuitry and concomitant relapse (30–32).

Dorsolateral PFC function is involved in working memory, attention, initiation of cognitive control, and conflict-induced behavioral adjustment (20,33–36). Studies have found decreased dlPFC activation after CBT for phobias (37) and depression (38). We found an inverse correlation between dlPFC activation and treatment retention: the less participants activated their dlPFC, the longer they stayed in treatment. This may reflect more efficient processing (39), leading to improved ability to access previous choices and adjusted

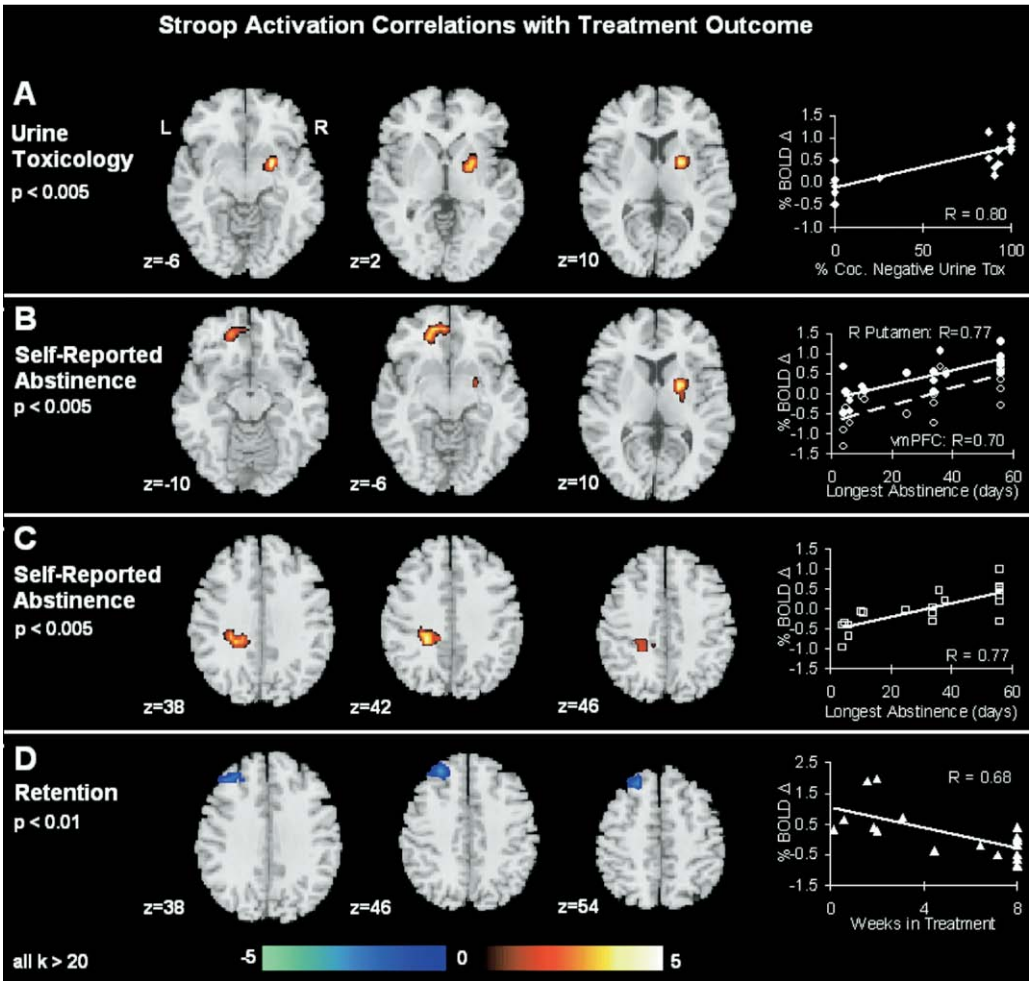

Figure 1. Regional brain activation during Stroop task performance correlates with treatment outcome measures. Brain slice correlation images of regional activation as denoted numerically in Table 3 (left side of figure) with corresponding percent signal change (right side of figure). **(A)** Percent cocaine negative urine toxicology over the course of treatment ($p < .005$), **(B)** and **(C)** longest duration of self-reported cocaine abstinence ($p < .005$), and **(D)** total weeks in treatment ($p < .01$). Red/white indicates areas of positive correlations between the indicated outcome measure and increased BOLD signal changes in the incongruent versus congruent contrast. Blue/green indicates areas of negative correlations between the indicated outcome measure and increased BOLD signal changes in the incongruent versus congruent contrast. Numbers indicate z axis MNI coordinates. Right side of brain is on the right. BOLD, blood oxygenation level-dependent; MNI, Montreal Neurological Institute.

behavioral decisions. Alternatively, this may represent less conflict arising in individuals who have committed to treatment (36). These and other possibilities warrant further investigation.

Regional Activations and Treatment Outcomes

Correlations between treatment, craving-related brain activation, and relapse have been previously examined in cocaine-dependent patients (26). Activation in the left precentral, superior temporal, posterior cingulate, and right middle temporal cortices during exposure to videotapes depicting cocaine use correlated with worse treatment effectiveness scores (26). The different nature of the task, intervention, and outcome measures may explain differences in brain activation patterns reported in the previous study compared with ours. However, similar to our findings, brain activations were more strongly correlated with relapse than were subjective reports of craving. These studies are in accord with an investigation finding that fMRI activation patterns in temporal, right insular, and posterior cortices during a simple two-choice decision-making task early in recovery predicted relapse in methamphetamine-dependent individuals (40). Together, these suggest that brain activation may be a more sensitive measure than self-report or task performance assessments for predicting treatment outcomes.

Strengths and Limitations

Strengths of this study include a sample where selection criteria, assessments, and outcomes were well defined and validated and participants were exposed to behavioral therapy with a strong empirical basis. The Stroop paradigm is well validated and has long been used to study cognitive control. Limitations include a relatively small sample size that received different treatments, a small number of incongruent trials, a short intertrial interval, and frequent co-occurring substance use disorders. However, the latter may provide greater face validity given comorbidities in this population (41). Future investigations should address limitations of the present study by using a single behavioral treatment and larger sample size. Larger samples may identify other brain regions, such as the insula, that have been implicated in other studies of drug dependence treatment outcome.

Conclusions and Future Directions

Treatment outcomes correlated with activation patterns of brain circuitry important in cognitive control, and the correlations appeared more robust and related to a broader range of measures than behavioral performance measures. These findings provide insight into neurobiological underpinnings of the treatment of cocaine dependence and hold promise to help target specific therapies for specific individuals and improve treatment outcomes.

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Supplementary material cited in this article is available online.

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