

Functional Neural Changes Following Behavioral Therapies and Disulfiram for Cocaine Dependence

Elise E. DeVito, Guangheng Dong, Hedy Kober, Jiansong Xu, Kathleen M. Carroll, and Marc N. Potenza
Yale University School of Medicine

A growing literature exists on neural correlates of treatment outcome. However, different types—or components of—treatment have distinct theorized mechanisms of action. And it is not yet known how changes in neural activity across treatment relate to engagement in different treatment components. Participants with cocaine use disorders in a randomized clinical trial received cognitive-behavioral therapy (CBT) plus, in a 2×2 design, contingency management (CM) or no CM, and disulfiram or placebo. Participants performed a functional MRI Stroop task, a measure of cognitive control, at the beginning of and after the 12-week treatment. Analyses assessed changes in Stroop-related neural activity within the sample overall and assessed how changes in Stroop-related activity correlated with measures of treatment process specific to each form of treatment (i.e., participation in CBT sessions, receipt of CM prizes, administration of disulfiram pills). Within the sample overall, compared with beginning of treatment, posttreatment Stroop-related neural activity was diminished in the hippocampus, thalamus, cingulate, precentral, post- and precentral gyrus, and precuneus and culmen regions ($p_{FWE} < .05$). In separate whole-brain correlation analyses, greater reductions in Stroop-related activity were associated with more treatment engagement—“CBT sessions” with the precentral gyrus, inferior parietal lobule, and middle and medial frontal gyrus; “CM prizes” with the postcentral frontal gyrus. Disulfiram “medication days” were not associated with changes in Stroop-related activity. Findings suggest that key process indicators of CBT and CM may be associated with functional changes in cognitive-control-related neurocircuitry.

Keywords: fMRI, cognitive-behavioral therapy, contingency management, disulfiram, cognitive control

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Cocaine use disorder (CUD) is associated with significant societal cost. Even with the best available treatments, many individuals with CUD cannot achieve or maintain abstinence (Substance Abuse and Mental Health Services Administration, 2014), highlighting the need for advancements in treatments. An understanding of the mechanism of action of treatments, including neurocognitive mechanisms, could lead to improvements in existing treatments or development of new

treatments (Chung et al., 2016; Insel & Gogtay, 2014). The aim of the current study is to make a preliminary attempt to relate changes in functional neural activity from beginning of treatment to posttreatment to engagement with different components of treatment for cocaine use. The treatment offered in this study was a mix of cognitive-behavioral therapy (CBT), contingency management (CM), and the medication disulfiram.

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Elise E. DeVito, Guangheng Dong, Hedy Kober, Jiansong Xu, and Kathleen M. Carroll, Department of Psychiatry, Yale University School of Medicine; Marc N. Potenza, Department of Psychiatry, Neurobiology, and Child Study Center, Yale University School of Medicine.

Guangheng Dong is now at Department of Psychology, Zhejiang Normal University.

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Correspondence concerning this article should be addressed to Elise E. DeVito, 1 Church Street, Suite 701, New Haven, CT 06510. E-mail: elise.devito@yale.edu

The treatments offered in this study are thought to have complementary clinical strengths and to address different aspects of substance use disorders (SUDs), and are hypothesized to have different mechanisms of actions. Combining several such treatments is widely accepted to improve clinical outcomes (Anton et al., 2006; National Institute on Drug Abuse, 2012; Sammons & Schmidt, 2001). For example, CBT (Carroll et al., 2004; Carroll, Nich, Ball, McCance, & Rounsaville, 1998), CM (Petry et al., 2005), and disulfiram (Carroll et al., 2004; Carroll et al., 1998) have each demonstrated enhancements in treatment efficacy relative to standard care alone, behavioral treatment controls, or placebo conditions in randomized clinical trials, and are thought to have complementary strengths and mechanisms. Specifically, CBT promotes abstinence by enhancing behavioral and cognitive coping skills as well as functional analyses of factors that contribute to continued drug use (Carroll, 1998). A strength of CBT is its durability (i.e., persistent efficacy after treatment ceases), perhaps related to the focus on skill building and greater cognitive control over craving and drug use behaviors (Carroll, Nich, Ball, et al., 2000). CM's strengths and limitations are complementary to CBT's. CM promotes treatment adherence and abstinence initiation by reinforcing target behaviors (e.g., treatment attendance, medication administration, cocaine abstinence) with money or prizes (Petry et al., 2005). As such, CM is a useful adjunct to enhance treatment adherence as well as initiate abstinence. However, CM's effects tend to weaken to some extent after the reinforcement schedule has ended. Although no pharmacotherapies have Food and Drug Administration indication for the treatment of CUD, disulfiram has shown promise in some trials (Carroll et al., 2004; Carroll, Nich, Ball, et al., 2000; Carroll, Nich, Shi, Eagan, & Ball, 2012; George et al., 2000; Kosten et al., 2013; Petrakis et al., 2000; Shorter et al., 2013). Although the mechanism underlying improved cocaine use outcomes with disulfiram is unknown, several potential mechanisms have been proposed (Barth & Malcolm, 2010; Carroll et al., 2004; Gaval-Cruz & Weinshenker, 2009), such as increasing plasma levels of dopamine by slowing the conversion of dopamine into noradrenaline via disulfiram's inhibition of dopamine- β -hydroxylase (D β H; Karamanakos, Pappas, Stephanou, & Marselos, 2001; Vaccari, Saba, Ruiu, Collu, & Devoto, 1996), reducing alcohol-precipitated relapses by inducing aversive responses to alcohol (Jørgensen, Pedersen, & Tonnesen, 2011), and altering cocaine's subjective reinforcing effects (Baker, Jatlow, & McCance-Katz, 2007).

One step toward investigating neurocognitive mechanisms of treatments for cocaine use could be to incorporate functional MRI (fMRI) measures into clinical trials for CUD. The fMRI task chosen should tap a cognitive domain, such as cognitive control, related to CUD. Disrupted cognitive control has been proposed to contribute to initiation and maintenance of CUD through poor attentional control, attentional biases toward drug-related stimuli, impaired response inhibition, and reduced ability to regulate craving (Garavan, Brennan, Hester, & Whelan, 2013; Garavan & Hester, 2007; Goldstein & Volkow, 2011; Lopez, Onyemekwu, Hart, Ochsner, & Kober, 2015). However, the pattern of drug-induced alterations in cognitive-control-related activity in SUDs is somewhat complex. Specifically, individuals with stimulant use disorders differ from non-substance-using individuals on task-related functional activity in a manner that is task and process specific; that is, the direction of difference (hypo- vs. hyperacti-

vation) and affected anatomical regions vary by task (for review, see Aron & Paulus, 2007; Crunelle, Veltman, Booij, Emmerik-van Oortmerssen, & van den Brink, 2012). For example, cognitive-control-related neural activity differs between active cocaine users and healthy comparison groups. Two separate studies comparing short-term abstinent (≤ 72 hr) cocaine users with healthy controls showed relatively decreased activity in cocaine users ($n = 15$) in anterior cingulate and right prefrontal regions and relatively increased activity in cerebellar regions while performing a go/no-go task with a working memory component (Hester & Garavan, 2004), whereas cocaine users ($n = 13$) performed worse on a go/no-go task and showed relatively lower activity in the anterior cingulate and right insula during successful stops and greater recruitment of medial frontal gyrus, left insula, and left inferior frontal gyrus (IFG) during errors (Kaufman, Ross, Stein, & Garavan, 2003). Individuals with CUD ($N = 14$) with confirmed short-term abstinence (> 72 hr), performing a multisensory Stroop task, showed greater recruitment of the left dorsolateral and ventrolateral PFC (dlPFC, vlPFC) and bilateral basal ganglia, and less deactivation of the bilateral ventromedial PFC (vmPFC), relative to nonusers ($n = 16$; Mayer, Wilcox, Teshiba, Ling, & Yang, 2013).

In addition, cognitive-control-related neural activity has been shown to be altered by acute cocaine administration (e.g., Garavan, Kaufman, & Hester, 2008) and may vary across abstinence duration (e.g., Connolly, Foxe, Nierenberg, Shpaner, & Garavan, 2012; Garavan et al., 2013). Finally, impairments on cognitive-control-related neuropsychological tasks may remain following abstinence (van Holst & Schilt, 2011). This may be consistent with some irreversible substance-use-related neural insult, or with premorbid vulnerabilities in brain systems (which may have preceded substance use) remaining following prolonged cessation of substance use. Taken together, these findings highlight the sensitivity of cognitive-control-related neural activity to CUD, cocaine use, and cocaine abstinence, but also illustrate the complexity of interpreting findings. In turn, this underscores the relevance of investigating these effects in the context of treatment.

Few studies have applied neuroimaging in the context of treatment for SUDs (for review, see Zilverstand, Parvaz, Moeller, & Goldstein, 2016), and several of those have demonstrated relationships between pretreatment cognitive-control-task-related brain activations and clinical outcomes (e.g., substance use during treatment or follow-up). For example, Color-Word-Stroop-related activity in CUD individuals ($n = 20$) initiating a range of treatments (sample combined from several randomized controlled trials [RCTs]) was associated with treatment outcome, such that greater pretreatment Stroop-related activity in the vmPFC, left posterior cingulate cortex, and right striatum correlated with longer duration of continuous abstinence during treatment (Brewer, Worhunsky, Carroll, Rounsaville, & Potenza, 2008). In addition, higher pretreatment Stroop-related activity in the striatum correlated with higher percent of drug-free urines during treatment, and lower pretreatment Stroop-related activity in the dlPFC correlated with longer treatment retention (Brewer et al., 2008). In another study, males with cannabis use disorder ($n = 20$) scanned prior to CBT and/or CM treatment showed diminished Stroop-related activity in regions including the dlPFC and ventral striatum relative to nonusers ($n = 20$; Kober, DeVito, DeLeone, Carroll, & Potenza, 2014). Furthermore, higher pretreatment Stroop-related activity in

the dorsal anterior cingulate cortex (ACC) and ventral striatum was associated with less cannabis use during treatment and 1-year follow-up, respectively (Kober et al., 2014). In individuals with CUD assessed at the beginning of inpatient detoxification treatment, higher right dorsal ACC activity during an attentional bias task (drug Stroop; $N = 34$; Marhe, Luijten, van de Wetering, Smits, & Franken, 2013) and lower error-related negativity (an electrophysiological measure of cognitive control; $N = 49$; Marhe, van de Wetering, & Franken, 2013) were each associated with more cocaine use at 3-month follow-up. In sum, this research relating pretreatment functional neural activity to drug use outcomes is important, but it does not directly address changes across treatment or relationships between neural activity and exposure to different treatment components.

A limited body of work has assessed changes in fMRI activity across treatment in substance users. One prior study from our group assessed change across behavioral treatment in a mixed substance-using outpatient sample ($N = 12$) receiving CBT or treatment as usual (DeVito et al., 2012). We found reduced Stroop-related activity after treatment relative to the beginning of treatment, in regions including the thalamus, midbrain, subthalamic nucleus, IFG, middle frontal gyrus (MFG), and ACC (DeVito et al., 2012). In that study, the sample size and study design limited our ability to relate changes in neural activity to components of treatment received. However, exploratory analyses within the regions of interest (ROIs) showing significant Stroop-related change across treatment suggested associations between greater reductions in Stroop-related activity (in left middle temporal gyrus and right MFG ROIs) and more exposure to CBT sessions (see the supplemental materials in DeVito et al., 2012). In another study in CUD, increases in drug-Stroop-related activity (a measure of attentional bias to drug stimuli) in the midbrain from baseline to 6-month follow-up ($N = 15$) was associated with fewer choices to view cocaine-related stimuli at follow-up (Moeller et al., 2012); however, because subjects were recruited from a range of treatment programs, the relative contribution of differential treatment components or types were not assessed.

Studies that have linked functional changes in stimulant users with specific pharmacotherapy have included 1-day laboratory trials of the medication rather than full clinical courses. For example, changes in Color-Word-Stroop-related activity were observed following administration of a single dose of methylphenidate (vs. placebo). In individuals with CUDs ($n = 16$) and nonusers ($n = 15$), methylphenidate reduced Stroop-related activity in the dorsal ACC and also reduced activity in the dlPFC in the CUD group only (Moeller et al., 2014). Individuals with methamphetamine use disorders ($n = 15$) exhibited increased Stroop-related activity, including in the dlPFC, parietal, and occipital regions relative to nonusers ($n = 18$), and methylphenidate further increased already hyperactive (relative to controls) Stroop-related activity in the dlPFC but reduced activity in the parietal and occipital regions (Jan et al., 2014). These findings suggest that the impact of treatment on Stroop-related activity may vary across different substance-using and healthy comparison groups. Taken together, the existing research supports the clinical relevance of cognitive-control-related functional activity by demonstrating its associations with treatment outcome and ability to change in response to treatment for SUDs. Focusing on changes over the treatment course that relate to exposure to components of specific

treatments is a novel approach to understanding mechanisms of action (Morgenstern, Naqvi, Debellis, & Breiter, 2013). This is important because effective therapies are hypothesized to change substance use by first changing brain-based cognitive processes related to substance use, including cognitive control. Prior work has demonstrated the efficacies of CBT, CM, disulfiram, or combinations of these treatments on reducing cocaine use in some individuals (Benishkek et al., 2014; Dutra et al., 2008; Pani et al., 2010). However, no studies have directly investigated (a) how changes in cognitive-control-related neural functioning over treatment may be associated with exposure to different treatment components, and (b) whether these treatment-component-related changes are distinct from functional brain changes associated with cocaine use outcomes.

The current study's goal was to extend prior work and relate exposure to different components of treatment to changes in cognitive-control-related fMRI activity from beginning of treatment to posttreatment in individuals with CUD. The Color-Word Stroop task, a measure of cognitive control, was chosen based on the proposed centrality of this cognitive construct to SUDs and abstinence. Data were drawn from participants in an RCT, all of whom received CBT as a platform treatment. Participants were also randomized to CM versus no-CM and to disulfiram versus placebo. The primary goal of the analyses was to identify how exposure to components of treatment was associated with changes in cognitive-control-related brain activity across treatment. First, we used a whole-brain analysis to assess how Stroop-related brain activity changed at posttreatment versus beginning of treatment in the sample overall. Second, we used separate whole-brain correlation analyses to assess how changes in Stroop-related brain activity at posttreatment versus beginning of treatment related to specific treatment components (number of CBT sessions, CM prizes, or days of disulfiram medication) and cocaine use measures (percent days cocaine abstinence during treatment; percent cocaine-negative urines during treatment). Based on our prior work in a mixed substance-using sample receiving CBT or treatment as usual, which showed reduced Stroop-related activity at post- relative to pretreatment in the thalamus, midbrain, subthalamic nucleus, IFG, MFG, and ACC (DeVito et al., 2012), we hypothesized that patients would show diminished Stroop-related brain activity at posttreatment relative to beginning of treatment in these regions. We hypothesized that greater reductions in Stroop-related activity would be observed in association with exposure to active ingredients of each treatment type as operationalized by process indicators as follows (see Table 1): (a) exposure to CBT skills training (CBT sessions attended), (b) access to reinforcement through CM (CM prizes drawn for abstinence or adherence to medication), and (c) exposure to disulfiram (total days of medication doses taken). Finally, we hypothesized, based on the structure and goals of the respective treatments (Potenza, Sofuoglu, Carroll, & Rounsaville, 2011), that CBT engagement specifically would be associated with greater efficiency (as indicated by lower Stroop-related activity at posttreatment vs. beginning of treatment) in regions associated with "top-down" regulatory control (e.g., ACC, IFG, MFG), and that CM engagement (i.e., randomization to CM group; more CM prizes drawn) would be associated with greater efficiency in regions that are involved in "bottom-up" circuitry (i.e., regions implicated in reward-processing and valuation, in-

Table 1
Definition of Treatment Engagement Variables

Treatment component	Treatment engagement variable	Operational definition of treatment variable
CBT exposure	CBT sessions	Number of CBT sessions attended during the 12-week treatment protocol. All subjects were invited to attend one 50-min CBT session per week during the 12-week protocol (i.e., total of up to 12 CBT sessions). CBT sessions were held individually with a clinician trained in CBT. Subjects could still remain active in the RCT if they failed to attend CBT sessions, so CBT sessions are not fully predicted by the number of weeks in treatment.
CM exposure	CM prizes	Number of CM prizes drawn during the RCT protocol, within the group randomized to CM treatment. Prizes were awarded for submission of urines as scheduled (thrice weekly) that were negative for cocaine and in-person observed administration of study pills as scheduled (thrice weekly). The number of prize draws increased for consecutive cocaine-negative urines and pill adherences and decreased following failure to provide a scheduled cocaine-negative urine sample (see Method and online supplemental materials for details).
Disulfiram exposure	Disulfiram medication days	Number of days of observed (during in person visit days) or self-reported (during take-home pill days) adherence to the medication protocol, within individuals randomized to disulfiram. During thrice-weekly sessions, subjects were observed taking their assigned pills and were given take-home doses of medications and asked to self-report their adherence to prior take-home medication days since last appointment.

Note. CBT = cognitive-behavioral therapy; CM = contingency management; RCT = randomized clinical trial.

cluding the striatum and ventromedial prefrontal cortex), which are also engaged by Stroop and other cognitive control tasks.

Method

Participants

Treatment-seeking participants were recruited to the fMRI study prior to treatment randomization in an RCT for CUD (Carroll et al., 2016). Participants were 18 years or older, recruited from a community-based outpatient treatment center, met *Diagnostic and Statistical Manual for Mental Disorders* (4th ed., text rev.; American Psychiatric Association, 2000) criteria for current cocaine dependence, and did not meet current dependence criteria for other illicit drugs. Other exclusion criteria included lifetime psychotic or bipolar disorder, current suicidal or homicidal ideation, or current medical condition that would contraindicate disulfiram treatment (e.g., hepatic or cardiac problems, hypertension, pregnancy). RCT participants were offered participation in the fMRI component if they did not report claustrophobia, colorblindness, history of severe head trauma with loss of consciousness, or metallic implants contraindicated in MRI. Of 99 RCT participants, 35 completed fMRI scans at in the beginning of treatment and following treatment, 26 of whom were included in the current fMRI analyses ($n = 9$ excluded because of delayed timing of scans relative to beginning of treatment or posttreatment, or insufficient treatment exposure; for details see the online supplemental materials). This study was approved by a human subjects institutional review board, and participants provided written informed consent prior to participation.

Treatment and Clinical Assessments

RCT methods are reported in full elsewhere (Carroll et al., 2016). Briefly, treatment lasted 12 weeks, and all participants were offered CBT. In addition, all participants included in the fMRI analyses were randomized to either disulfiram ($n = 10$) or placebo ($n = 16$) and CM ($n = 14$) or no-CM ($n = 12$) in a

factorial design, resulting in four treatment conditions: (a) CBT + CM + disulfiram ($n = 4$), (b) CBT + CM + placebo ($n = 10$), (c) CBT + disulfiram ($n = 6$), and (d) CBT + placebo ($n = 6$). Participants were asked to attend the clinic three times per week during the 12-week protocol; medication was dispensed and urine specimens were collected at each clinic visit. All in-person treatment delivery, tracking of treatment adherence, and tracking monitoring of substance use occurred in those thrice-weekly visits. Because of the limited sample sizes for the four treatment cells within the fMRI sample, analyses focused on the entire sample or comparing disulfiram versus placebo, or CM versus no-CM.

Cognitive-behavioral therapy (CBT). Weekly 50-min individual CBT sessions were offered as per the CBT manual (Carroll, 1998), delivered by doctoral-level clinicians with CBT experience and demonstrated competence (Carroll, Nich, Sifry, et al., 2000). The primary process indicator for CBT was number of CBT sessions attended (see Table 1). CBT aims to promote abstinence by teaching and promoting practice of behavioral and cognitive control strategies (e.g., coping with craving, improving decision-making skills). CBT homework, assigned at each session, offers the opportunity to practice applying the skills discussed in CBT sessions.

Contingency management (CM). All participants were randomly assigned to receive CM (CM group) or not (no-CM group). Those assigned to CM could draw at least one prize chance from a bowl each time they demonstrated abstinence (submitted a cocaine-free urine specimen) or pill adherence (staff witnessed ingestion of study capsule). Consistent with previously established procedures, the number of CM draws per reinforced behavior (abstinence, pill adherence) escalated (up to a maximum of seven draws) with each consecutive demonstration of abstinence or adherence. If patients missed a scheduled visit or failed to submit a cocaine-negative urine, the number of prize draws for subsequent reinforced behaviors would drop back down to one (for CM method details, see the online supplemental materials and Carroll et al., 2016; Petry, 2000; Petry et al., 2005). The primary process indicator for exposure to CM in these

analyses was the sum of total prizes drawn across treatment (“number of CM prizes”; Table 1).

Disulfiram. All participants were randomly assigned to either disulfiram (250 mg daily) or identical placebo capsules, administered in a double-blind manner. This disulfiram dose was associated with reduced cocaine use in previous trials (Carroll et al., 2004). Medication or placebo pill adherence was tracked by observed medication administration at thrice-weekly visits, plus patient self-report for take-home doses. This combination of observed and self-reported adherence was used as the primary process indicator (“days of medication”; Table 1) for disulfiram treatment within the group randomized to disulfiram. A riboflavin tracer in the pills indicated high consistency with self-report (Carroll et al., 2016). All participants were warned of negative consequences of drinking alcohol on disulfiram, strongly discouraged from drinking alcohol during the study, and told that their capsules would be withheld if their breath samples tested positive for alcohol.

Substance use assessments. Baseline assessments included the Addiction Severity Index (ASI; McLellan et al., 1992). Thrice weekly during treatment, participants were assessed with urine toxicology and alcohol-breath screens, and had study capsules dispensed (disulfiram or placebo) and clinical symptoms monitored. Self-reports of day-by-day use of cocaine, alcohol, and other drugs were collected weekly during treatment, using the timeline followback method (Robinson, Sobell, Sobell, & Leo, 2014; Sobell & Sobell, 1992). When sessions were missed or the participant did not complete treatment, self-report data were collected for the missed data collection days at subsequent sessions. Adverse events and blood pressure were tracked weekly during treatment. Consistent with our prior work (Carroll et al., 2014, 2016), primary clinical outcome variables were percent of cocaine-negative urines and self-reported days of abstinence during treatment.

Clinical Data Analyses

Indicators of cocaine use within treatment were assessed with ANOVAs including medication (disulfiram, placebo) and CM (CM, no-CM) as between-subjects factors (see Table 2). Clinical outcomes for the parent RCT sample are reported elsewhere (Carroll et al., 2016). Briefly, there were consistent effects favoring CM over no-CM, with mixed findings for disulfiram.

fMRI Methods

Participants were administered a measure of cognitive control, the event-related fMRI Color-Word Stroop task (DeVito et al., 2012; Kober et al., 2014), on two occasions: prior to or in the beginning of treatment (days between start of study treatment and beginning-of-treatment scan: $M = 3$ days, $SD = 5$, range = 6 days prior to treatment start to 12 days into treatment) and following the end of the 12-week treatment (i.e., posttreatment and prior to 3-month follow-up; days between end of treatment and posttreatment scan: $M = 20$ days, $SD = 20$, range = 1–61 days). On each trial, participants were asked to name the ink color of color words presented in congruent (e.g., “RED” in red ink) or incongruent colors (e.g., “RED” in blue ink; see the online supplemental methods for task details).

Stroop mean response times, collected out of scanner at time of scanning, were analyzed in SPSS with mixed-model ANOVAs including session (beginning of treatment, posttreatment) and trial

type (incongruent, congruent) as within-subject factors, and medication (disulfiram, placebo) and CM (CM, no-CM) conditions as between-subjects factors. Stroop errors on incongruent trials were analyzed with mixed-model ANOVAs including session as a within-subject factor, and medication and CM conditions as between-subjects factors.

fMRI data acquisition and preprocessing steps were consistent with our prior work (e.g., Kober et al., 2014; see the online supplemental methods for details). For second-level random-effects analyses, the contrast of interest was the “change in Stroop effect,” calculated as $[(\text{Incongruent}_{\text{post}} > \text{Congruent}_{\text{post}}) > (\text{Incongruent}_{\text{pre}} > \text{Congruent}_{\text{pre}})]$, which assessed changes in Stroop-effect-related activity at posttreatment versus beginning of treatment (DeVito et al., 2012). fMRI results were family-wise error-corrected at two-tailed $p_{\text{FWE}} < 0.05$.

To address the primary research question regarding how neural correlates of cognitive control change across treatment and how these changes relate to engagement with different treatment components, the following approach was taken. First, changes in fMRI Stroop effect were assessed at the whole-brain level (Table 3A). Second, separate whole-brain correlation analyses were carried out between the “change in Stroop effect” contrast and the following indicators of treatment engagement: (a) CBT sessions (entire sample, $N = 26$), (b) CM prizes drawn (subsample randomized to CM, $n = 14$), and (c) days of study medication taken (subsample randomized to disulfiram, $n = 10$; description of variables are in Table 1; results are in Table 3B). All analyses were familywise error-corrected for multiple comparisons ($p_{\text{FWE}} = .05$).

Because level of cocaine abstinence during treatment could affect “change in Stroop effect” across treatment, a separate whole-brain correlation was run between the “change in Stroop effect” contrast and cocaine use within treatment (i.e., percent days self-reported abstinence during treatment; percent cocaine-negative urines during treatment; Table 3B). To check whether the regions associated with engagement in different aspects of treatment overlapped or were simply reflections of the same regions associated with cocaine abstinence during treatment, the separate correlation analyses were entered into formal conjunction analyses (see the online supplemental materials for detailed methods). For all fMRI correlation analyses, if variables were not normally distributed, rank-order correlations were used as a nonparametric alternative.

Additional analyses addressed whether “change in Stroop effect” differed by randomly assigned treatment condition in separate analyses: (a) CM versus no-CM groups, and (b) disulfiram versus placebo groups. Because treatment group differences in “change in Stroop effect” could be influenced by beginning-of-treatment group differences, potentially confounding beginning-of-treatment differences between treatment, groups were assessed by comparing beginning-of-treatment Stroop-effect ($\text{Incongruent}_{\text{pre}} > \text{Congruent}_{\text{pre}}$ trials) by CM ($\text{CM} > \text{no-CM}$) and medication ($\text{disulfiram} > \text{placebo}$) randomization status.

Results

Beginning-of-Treatment Clinical Characteristics, Treatment Engagement, and Cocaine Use Outcomes

There were no significant treatment group differences on demographic, baseline clinical, or treatment engagement measures, with

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Table 2
Baseline Demographic, Psychiatric, and Substance Use Characteristics and Stroop Behavior by Treatment Group

Baseline, clinical outcome and stroop behavior variables	Contingency management (n = 14)		No contingency management (n = 12)		Statistics <i>F(p)</i> ^e	
	Total sample (n = 26)	Placebo (n = 10)	Disulfiram (n = 4)	Placebo (n = 6)	Disulfiram (n = 6)	CM Status × Disulfiram Status
Demographics						
Sex (Female), <i>N</i> (%)	10 (38.5)	3 (30.0)	3 (75.0)	2 (33.3)	2 (33.3)	1.14 (.29)
Age	40.27 (7.55)	41.00 (6.90)	42.00 (2.94)	38.33 (11.26)	39.83 (7.71)	.01 (.94)
Race, <i>N</i> (%)						
Caucasian	10 (38.5)	2 (20.0)	2 (50.0)	3 (50.0)	3 (50.0)	
African American	12 (46.2)	6 (60.0)	2 (50.0)	2 (33.3)	2 (33.3)	
Hispanic	2 (7.7)	0 (0)	0 (0)	1 (16.7)	1 (16.7)	
Multiracial/Other	2 (7.7)	2 (20.0)	0 (0)	0 (0)	0 (0)	
Estimated IQ (SILS)	97.80 (10.77)	98.33 (10.33)	93.25 (8.77)	96.33 (13.84)	101.50 (10.60)	2.12 (.16)
Number of months incarcerated, lifetime	25.38 (52.88)	37.20 (65.94)	3.00 (6.00)	5.83 (11.94)	40.17 (67.75)	2.40 (.14)
Other lifetime psychiatric diagnoses, <i>N</i> (%)						
Alcohol use disorder	16 (61.5)	5 (50.0)	3 (75.0)	4 (66.7)	6 (100.0)	.00 (1.00)
Major depression	7 (26.9)	7 (70.0)	0 (0)	1 (16.7)	3 (50.0)	1.39 (.24)
Anxiety disorder	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	.00 (1.00)
Antisocial personality disorder	2 (7.7)	0 (0)	0 (0)	0 (0)	2 (33.3)	.00 (1.00)
Days of use in month prior to treatment^a						
Cocaine	14.88 (7.80)	13.50 (7.69)	17.50 (8.81)	16.83 (8.95)	13.50 (7.40)	.01 (.92)
Alcohol	7.35 (8.38)	5.80 (7.22)	14.25 (11.90)	6.67 (9.75)	6.00 (5.62)	1.28 (.27)
Cannabis	2.12 (5.55)	.40 (.97)	7.00 (14.00)	2.67 (2.66)	1.17 (1.17)	1.31 (.26)
Cigarettes	20.73 (11.89)	18.80 (13.21)	21.00 (14.00)	23.33 (11.43)	21.17 (11.36)	.00 (1.00)
Lifetime years of regular use						
Cocaine	9.31 (6.18)	7.60 (4.25)	10.75 (6.99)	9.33 (8.89)	11.17 (6.18)	.17 (.69)
Alcohol	8.69 (9.01)	3.90 (4.95)	9.00 (8.60)	13.67 (11.60)	11.50 (9.85)	3.02 (.10)
Cannabis	5.81 (7.38)	2.30 (3.37)	1.50 (2.38)	7.17 (6.37)	13.17 (10.05)	.17 (.68)
Treatment engagement						
Days in treatment	59.77 (30.22)	44.60 (29.14)	80.50 (7.00)	49.67 (38.51)	81.33 (6.53)	1.05 (.32)
Number of CBT sessions attended	6.73 (4.28)	5.20 (4.24)	8.25 (2.87)	6.17 (5.42)	8.83 (3.55)	.07 (.79)
Number of days of disulfiram doses taken	N/A	N/A	39.70 (25.81)	45.00 (34.18)	45.00 (34.18)	2.06 (.12)
Number of CM prizes drawn	N/A	82.30 (88.87)	120.50 (84.03)	N/A	N/A	N/A
Treatment outcome						
% Days self-reported abstinence within treatment period	81.50 (22.50)	92.62 (7.48)	59.23 (45.00)	76.39 (19.39)	82.94 (12.73)	.19 (.66)
% Urines negative for cocaine within treatment period	44.87 (39.78)	67.74 (34.19)	35.64 (45.24)	16.50 (27.53)	41.29 (41.55)	2.30 (.14)
Stroop task behavior^b						
Beginning of treatment						
Mean congruent trial RT (ms)	508.88 (124.40)	537.27 (120.59)	436.51 (125.42)	506.07 (121.09)	521.59 (157.83)	—
Mean incongruent trial RT (ms)	637.30 (208.80)	691.27 (209.99)	574.74 (221.48)	597.74 (187.61)	642.76 (304.05)	—
Percent incongruent errors	22.58 (19.64)	28.14 (26.12)	15.71 (16.41)	23.33 (19.24)	17.14 (5.71)	—
Posttreatment						
Mean congruent trial RT (ms)	517.27 (132.25)	477.15 (113.64)	463.05 (53.16)	560.90 (137.53)	577.23 (177.49)	—
Mean incongruent trial RT (ms)	639.87 (211.44)	593.14 (210.29)	547.90 (116.71)	701.69 (240.86)	719.79 (241.08)	—
Percent incongruent errors	23.10 (23.02)	30.21 (33.00)	15.00 (15.36)	18.57 (8.62)	21.19 (17.06)	—

Note. Results are reported as mean (*SD*) unless otherwise noted, in which case it is reported as *N* (%). CM = contingency management; SILS = Shipley Institute of Living Scale; CBT = cognitive-behavioral therapy; RT = response time; ms = milliseconds; N/A = not applicable; CM = contingency management.

^a Days of use in month prior to treatment was out of a possible total of 28 days (i.e., past 4 weeks). ^b Stroop task behavior analyzed with mixed-model ANOVAs including session (beginning of treatment, posttreatment) and trial type (incongruent, congruent) as within-subject factors, and medication (disulfiram, placebo) and CM (CM, no-CM) conditions as between-subject factors (trial type, *F* = 58.99, *p* < .001; no other significant main or interactive effects). Stroop errors on incongruent trials were analyzed with mixed-model ANOVAs including session as a within-subject factor, and medication and CM conditions as between-subject factors (no significant main or interactive effects). ^c Statistics *F(p)* showing comparisons by CM Status (randomized to CM vs. No CM), Disulfiram Status (randomized to disulfiram vs. placebo), and CM Status by Disulfiram Status interactions. Statistics in bold indicate statistical significance (*p* < 0.05). ^d Bold values showing a significant difference in lifetime years of cannabis use between those randomized to contingency management versus no CM. ^e Bold values showing a significant difference in days in treatment between those randomized to disulfiram versus placebo. ^f Bold values showing a significant interaction in days self-reported abstinence during treatment by CM Status and Disulfiram Status.

Table 3
fMRI Stroop Changes at Posttreatment vs. Beginning of Treatment and Associations With Treatment Components

Cluster label (peak)	Regions of activation	Peak coordinates			Statistics (<i>t</i> value)		
		R/L	x	y	z	Maximum voxel	Cluster mean
A. Change in fMRI Stroop effect at posttreatment vs. beginning of treatment (Trial Type [inc, con] × Session [post, beginning]), <i>N</i> = 26							
Culmen	L culmen, L parahippocampal gyrus	L	-9	-36	-9	-5.45	-3.29
Precuneus	L precuneus, L lingual gyrus, L posterior cingulate	L	-9	-60	24	-5.05	-3.29
Cingulate gyrus	R/L cingulate gyrus	R	9	9	42	-4.63	-3.30
Postcentral gyrus	R postcentral gyrus, R precentral gyrus	R	39	-18	33	-4.57	-3.14
Angular gyrus	L angular gyrus, L middle temporal gyrus, L superior temporal gyrus	L	-33	-75	36	-4.52	-3.27
Thalamus	L and R thalamus, R caudate	L	-3	0	0	-4.51	-3.20
Hippocampus	R hippocampus, R amygdala, R parahippocampal gyrus, lentiform nucleus	R	30	-21	-15	-4.28	-3.23
Precentral gyrus	R precentral gyrus	R	60	6	3	-3.99	-3.14
B. Whole-brain correlations between “change in fMRI Stroop effect” and treatment engagement and outcome							
i. Correlation between “change in fMRI Stroop effect” and number of CBT sessions (<i>N</i> = 26)							
Precentral gyrus	L precentral gyrus	L	118	-36	-15	-75	-.55
Inferior parietal lobule	R inferior parietal lobule	R	74	33	-36	-73	-.56
Middle frontal gyrus	L middle frontal gyrus	L	61	-42	33	-72	-.57
Medial frontal gyrus	R medial frontal gyrus, L/R precentral gyrus, L/R superior frontal gyrus	R	194	6	-15	-70	-.55
ii. Correlation between “change in fMRI Stroop effect” and total number of contingency management prizes (within CM group, <i>n</i> = 14)							
Postcentral	R postcentral	R	51	45	-18	-93	-.73
Postcentral	L postcentral, L precentral gyrus	L	58	-33	-24	-91	-.73
iii. Correlation between “change in fMRI Stroop effect” and number of days of disulfiram treatment taken (<i>n</i> = 10)							
No significant clusters							
iv. Correlation between “change in fMRI Stroop effect” and percent days cocaine abstinence during treatment period (<i>N</i> = 26)							
Superior temporal gyrus	R superior temporal gyrus, R transverse temporal gyrus	R	63	-12	12	.72	.55

Note. All results presented survive family-wise error correction for multiple comparisons at the whole-brain level to two-tailed $p_{FWE} < .05$. Section A shows clusters that survived corrections for multiple comparisons that showed a change in Stroop effect-related activity in the sample overall at posttreatment versus beginning of treatment (*N* = 26). Section B shows clusters that survived corrections for multiple comparisons from separate whole-brain rank-order nonparametric correlations with the change in Stroop effect contrast and measures of treatment engagement (i. Number of CBT sessions, *N* = 26; ii. Total number of CM prizes within those randomized to CM, *n* = 14; iii. Number of days of disulfiram treatment taken within those randomized to medication, *n* = 10); and within-treatment cocaine use (iv. Percent days cocaine abstinence during the treatment period, *N* = 26). The figures that correspond to the these results are as follows: For Section A, see Figure 1A, extracted cluster means in Figure 1B; and “whole-brain” slice-out images in online Supplemental Figure 2 (as well as full slice-out images for the beginning of treatment Stroop effect and posttreatment Stroop effect contrasts separately in online Supplemental Figure 1). For Section B, see Figure 2 and “whole-brain” slice-out images in online Supplemental Figure 3. fMRI = functional MRI; Inc = incongruent trials; Con = congruent trials; Beginning = beginning of treatment; Post = posttreatment; R = right; L = left; k = cluster size (in voxels); CM = contingency management; CBT = cognitive-behavioral therapy.

two exceptions: There were more years of cannabis use in no-CM versus CM groups, and more days in treatment in the disulfiram versus placebo groups (see Table 2). Despite no main effects of group on cocaine-use outcomes in this fMRI subsample, a significant CM \times Medication Condition interaction on “percent days self-reported cocaine abstinence” during treatment indicated best cocaine use outcomes in the CM/placebo group, worst outcomes in the CM/disulfiram group, and intermediate outcomes in the no-CM groups (see Table 2). This pattern is slightly different than that of the full RCT sample, wherein cocaine use outcomes were best in the CM/placebo group, worst in the no-CM/placebo group, and intermediate in the disulfiram groups (Carroll et al., 2016).

Stroop Behavior

The expected behavioral Stroop effect was indicated by a main effect of trial type on response times, reflecting slower correct response times for incongruent versus congruent trials (trial type, $F[1, 15] = 58.99, p < .001$). There were no main or interactive effects of group (CM, No CM; disulfiram, placebo) or session (posttreatment, beginning of treatment) on response time errors during incongruent trials (see Table 2).

Changes in fMRI Stroop and Relationship to Treatment Engagement and Outcome

Within the whole sample (across treatment groups; $N = 26$), there were significant reductions in Stroop-related neural activity from beginning of treatment to posttreatment in the hippocampus,

thalamus, cingulate, precentral gyrus, postcentral gyrus, precuneus, and culmen clusters (see Table 3A; Figure 1A, B; online Supplemental Figure 2 for additional views; and online Supplemental Figure 1 for Stroop-related activity at beginning of treatment and posttreatment). This is consistent with our prior work (DeVito et al., 2012).

Whole-brain correlations between “change in Stroop effect” and treatment engagement revealed negative correlations, showing that greater reductions in Stroop-related activity at posttreatment (relative to beginning of treatment) were associated with greater treatment engagement. Importantly, this pattern was apparent in different regions, depending on the specific treatment engagement measure (Table 3B; Figure 2). Specifically, attendance at more CBT sessions was associated with a greater reduction in Stroop-related activity in the precentral gyrus, inferior parietal lobule (IPL), MFG, and medial frontal gyrus, and more earned CM prizes were associated with greater reduction in postcentral gyrus. In contrast, days of disulfiram medication taken was not significantly associated with changes in Stroop fMRI. Better cocaine use outcomes during treatment (higher percent days of cocaine abstinence during treatment) was positively associated with increases in Stroop-related activity in the superior temporal gyrus. There were no significant correlations between changes in Stroop fMRI and cocaine negative urines. Conjunction analyses revealed that the regions associated with cocaine use outcomes did not overlap with regions associated with treatment engagement measures, and regions associated with different aspects of treatment engage-

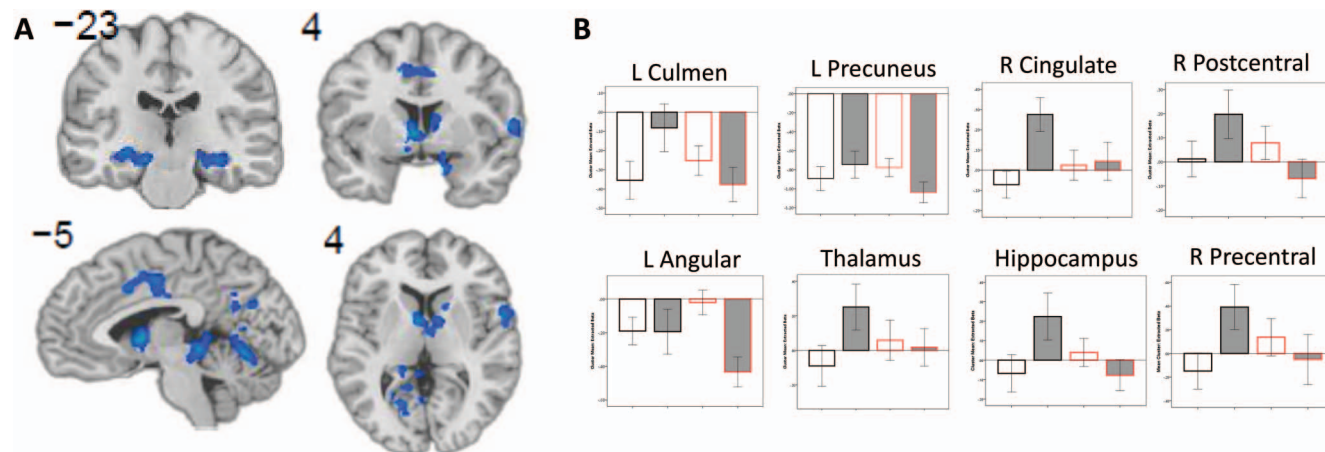


Figure 1. Reduced Stroop-related activity at posttreatment versus beginning of treatment. (A) Changes in Stroop-effect-related activity (incongruent > congruent trials) at posttreatment versus beginning of treatment in the sample overall ($N = 26$). Blue (or dark gray, in gray scale) indicates regions with lower Stroop-related BOLD signal at posttreatment relative to beginning of treatment. fMRI results are family-wise error-corrected for multiple comparisons at $p_{FWE} < .05$. For additional details, see Table 3A. For full results, see online Supplemental Figure 2. (B) The mean extracted betas from significant clusters (significant clusters shown in Section A, in full in online Supplemental Figure 2, and reported in Table 3A). Mean betas are presented for each trial type (incongruent, congruent) and time point (beginning of treatment, posttreatment) relative to all unmodeled baseline. Bars are in the following order: congruent (beginning of treatment), incongruent (beginning of treatment), congruent (posttreatment), incongruent (posttreatment). Fill color indicates trial type (white = congruent; gray = incongruent). Border color indicates time point (black = beginning of treatment; red = posttreatment). Error bars represent ± 1 SEM. L = left, R = right. See the online article for the color version of this figure.

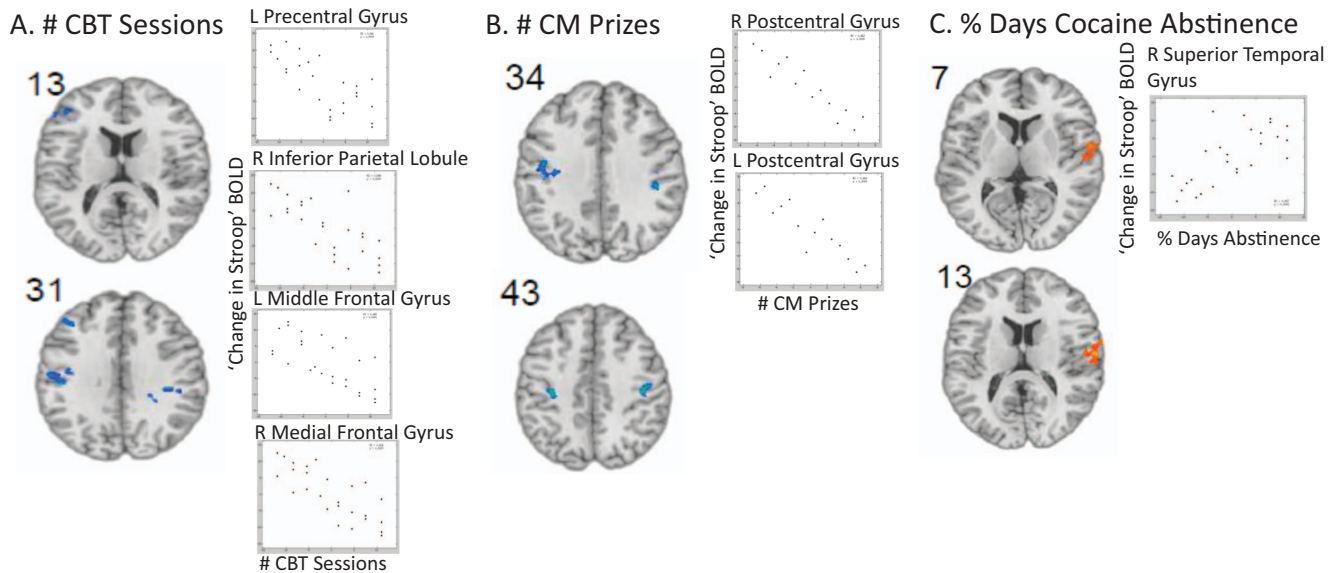


Figure 2. Correlation between change in Stroop effect and treatment engagement and outcome. Rank-order whole-brain correlations between “change in Stroop effect”-related activity at posttreatment versus beginning of treatment ($[\text{Incongruent}_{\text{post}} - \text{Congruent}_{\text{post}}] - [\text{Incongruent}_{\text{pre}} - \text{Congruent}_{\text{pre}}]$) and (A) number of cognitive-behavioral therapy (CBT) sessions attended ($N = 26$); (B) number of contingency management (CM) prizes received, within group randomized to CM ($N = 14$); and (C) percent days of self-reported days of cocaine abstinence during treatment. Blue regions indicate inverse correlations showing lower Stroop-related activity at posttreatment versus beginning of treatment associated with more treatment engagement. Red regions indicate positive correlations showing higher Stroop-related activity at posttreatment versus beginning of treatment associated with more cocaine abstinence. Scatterplots show extracted rank order correlations from each significant cluster (see Table 3B). fMRI results are family-wise error-corrected for multiple comparisons at $p_{\text{FWE}} < .05$. For full slice-out of results, see online Supplemental Figure 3. See the online article for the color version of this figure.

ment (CBT, CM or disulfiram) did not overlap (see online supplemental materials for detailed results).

Analyses comparing changes in Stroop effect from beginning of treatment to posttreatment by treatment group did not reveal any significant differences between CM versus no-CM or disulfiram versus placebo groups. Further, there were no significant differences in fMRI Stroop-related neural activity at beginning of treatment by CM or disulfiram group status, which was investigated as a potentially confounding factor.

Discussion

Cognitive control is considered a key process in SUDs (Garavan et al., 2013; Garavan & Hester, 2007; Potenza et al., 2011; Sofuoglu, DeVito, Waters, & Carroll, 2013). This study is the first to investigate relationships between cognitive-control-related neural activity and indicators of exposure to putative active ingredients of treatment in individuals with CUDs. Findings partially supported our hypotheses. Consistent with our hypotheses for the first analytic approach, greater treatment engagement was associated with greater reduction in Stroop-related activity. Importantly, engagement with different treatment components (e.g., exposure to CBT or CM components) was correlated with reductions in Stroop-related activity across different cognitive-control-related regions—consistent with the conceptualization of these components as theoretically and mechanistically distinct. However, engagement with

disulfiram was not associated with change in Stroop-related activity in these regions. The patterns of associations between treatment engagement and changes in Stroop-related activity were in distinct regions from those associated with cocaine use during treatment, suggesting these associations were not simply a reflection of cocaine use outcomes.

In contrast with our hypotheses for the second analytic approach, no treatment group (CM vs. no-CM; disulfiram vs. placebo) differences in “change in Stroop effect” survived corrections for multiple comparisons at the whole-brain level. Out-of-scanner behavioral Stroop performance did not significantly change across treatment. Although this lack of significant improvement could be seen as a limitation, it is also a strength, allowing interpretation of improved neural efficiency in the context of relatively stable behavioral performance. Designing fMRI studies to match groups behaviorally such that the neural activity can be directly compared is a well-established method when cognitive impairment is expected in one group (e.g., Casey, Tottenham, Liston, & Durston, 2005).

In the sample overall, we found diminished Stroop-related activity posttreatment compared with beginning of treatment. This pattern of change is consistent with our prior findings in a mixed substance-abusing sample receiving CBT or treatment as usual (DeVito et al., 2012). Regions showing reduced Stroop-related activity in the overall sample have previously been shown to

exhibit task-related functional differences between individuals with CUD and non-substance-using comparisons, using tasks tapping similar cognitive constructs as the Stroop (Elton et al., 2014; Hester & Garavan, 2004; Kaufman et al., 2003). Prior research provides context for interpreting such diminished activity following treatment.

Decreased task-related activity following treatment may reflect improved efficiency. For example, although increased task difficulty and attentional load have been associated with increased task-related activity, practice is known to reduce task-related activity, which suggests improved efficiency (e.g., Tomasi, Ernst, Caparelli, & Chang, 2004). Furthermore, practice effects are associated with decreased precuneus activation, and individuals with CUD show less practice-effect-related deactivation than healthy comparison subjects, suggesting that greater practice-related decreases in functional activity may be more optimal (Goldstein et al., 2007).

Changes in task-related activity following treatment may also relate to changes in cocaine use, because cognitive-control-related functional activity is altered by acute cocaine administration and across cocaine abstinence. For example, acute intravenous administration of cocaine prior to go/no-go increased fMRI task-related neural activity in a manner that partially “normalized” functional activity in active cocaine users (Garavan et al., 2008). More specifically, following intravenous injection of cocaine (relative to intravenous saline), active cocaine users had higher successful-inhibition-related activity in right the insula/IFG and right MFG, and higher error-related activity in the right posterior cingulate/lingual gyrus, the culmen of vermis/left lingual gyrus, the left IPL, and the right middle frontal gyrus, and decreased activity in the left posterior cingulate on a go/no-go task. When compared with healthy participants from a prior study, and using the same ROIs that had previously shown reduced activity in cocaine users (Kaufman et al., 2003), the findings were replicated in this group of cocaine users on saline indicating that cocaine users showed go/no-go-related hypoactivation following intravenous (IV) saline, relative to healthy controls, and that IV cocaine increased task-related activity in overlapping regions and abolished the significant hypoactive differences (relative to healthy controls; Garavan et al., 2008). Furthermore, response-inhibition-related activity is altered nonuniformly throughout abstinence (Garavan et al., 2013), and prior findings from cross-sectional studies remain somewhat mixed. For example, in a cross-sectional study comparing healthy nonusers, shorter-term-abstinent (1–5 weeks), and longer-term-abstinent (40–120 weeks) cocaine users, fMRI go/no-go task-related activity differed across groups in several brain regions (Connolly et al., 2012). However, longer duration of abstinence was not necessarily associated with a change toward normalization (i.e., becoming closer to the healthy control group); rather, neural activity in some regions was more “abnormal” in the longer-term-abstinence group, which might reflect compensation (Connolly et al., 2012).

Furthermore, one study found no statistically significant group differences in fMRI go/no-go between healthy controls ($n = 45$) and cocaine-abstinent individuals (average abstinence = 32.3 weeks; range <1–100 weeks) who were recruited from intensive inpatient treatment for cocaine use disorder ($n = 27$; Bell, Foxe, Ross, & Garavan, 2014). In contrast, a separate Go/No-Go fMRI study found no group differences during successful inhibitions, but

during commission errors found that both current ($N = 30$) and former cocaine users ($N = 29$; average duration of abstinence 51.2 weeks) differed from healthy controls ($N = 35$), with former cocaine users showing differences from healthy controls in more a priori regions of interest than current cocaine users (Castelluccio, Meda, Muska, Stevens, & Pearson, 2014). However, cocaine use or abstinence did not appear to be substantial factors driving the current findings, as changes in Stroop-related BOLD-signal measures within treatment did not correlate with activity in the same regions as did measures of cocaine abstinence during treatment.

When interpreting the pattern of change in task-related activity following treatment, it may be important to note that clinical improvements may not always be accompanied by functional changes in the direction of “normalization.” Rather, substance use treatments may act through both adaptation and normalization of functional activity. For example, modafinil further increased hyperactive task-related functional activity in the ACC in cocaine users, relative to non-substance-using comparisons, and this increased activity was associated with diminished cocaine-craving (Goudriaan, Veltman, van den Brink, Dom, & Schmaal, 2013). Furthermore, duration of abstinence is not necessarily associated with a change toward normalization (i.e., becoming closer to the healthy control group; Connolly et al., 2012). This may reflect the complex interplay between preexisting vulnerabilities and drug-induced neuroadaptation in substance users. Namely, premorbid functional abnormalities may confer vulnerability to SUDs, and drugs may have acute and prolonged effects on brain function, and some drug-induced abnormalities may persist through prolonged abstinence. Therefore, abstinence may not return individuals to pre-substance-use-disorder baselines, and premorbid baselines may be suboptimal treatment targets as they may not represent normalizations of functional activity relative to healthy non-drug-users with low SUD vulnerability (see Moeller, Bederson, Alia-Klein, & Goldstein, 2016, for review of changes with substance use onset and predictors of treatment outcome). These complexities underline the limits of using healthy case comparisons to derive treatment target, and reinforce the importance of testing treatment-related change within substance abusers and relating these changes to treatment mechanisms. However, taken together, greater diminishment of Stroop-related activity across treatment and its association with exposure to treatment components could be consistent with greater improvements in efficiency with more treatment exposure.

Clinical Implications and Mechanisms of Action

Within the thalamus, failed-inhibition-related activity is greater in individuals with CUD in earlier versus later stages of abstinence and positively associated with subjective feelings of loss of control (Li et al., 2010). Thalamocortical connectivity is important in bottom-up cognitive-control in CUD (Worhunsky et al., 2013). Performance-monitoring, including error-processing and behavioral adjustment, is crucial to successful cognitive control (Taylor, Stern, & Gehring, 2007) and is impaired in cocaine-dependent individuals (Garavan & Stout, 2005). The ACC has been implicated in cocaine craving (Garavan et al., 2000) and has a well-established role in response conflict monitoring (Barch et al., 2001). Thus, our findings of reduced Stroop-effect-related thalamic and cingulate activity at posttreatment relative to beginning of treatment in the sample overall may be consistent with greater

efficiency of cognitive control and performance monitoring following treatment.

The medial frontal gyrus has been implicated in the cognitive regulation of craving (Kober et al., 2010). Training in recognizing and coping with craving is central to CBT. Therefore, correlations between greater reductions in Stroop-related activity in the medial frontal gyrus and more CBT sessions attended, but not other treatment components, may be consistent with top-down regulation of attention-related processes as a treatment mechanism of CBT (Potenza et al., 2011)

Disulfiram doses did not correlate with change in cognitive-control-related activity in any clusters. This may reflect the weak therapeutic efficacy of disulfiram in this RCT (Carroll et al., 2016) and moderate efficacy in prior trials (Pani et al., 2010), and may suggest that disulfiram's therapeutic mechanism of action is not likely related to cognitive control. However, a larger sample of individuals receiving disulfiram is needed to make more definitive statements.

Limitations

Strengths of this manuscript include availability of beginning-of-treatment and posttreatment fMRI data from a factorial RCT testing three well-systematized evidence-based therapies, which also included objective indices of treatment process. The principal limitation is the small sample size, which limited power and precluded a full mediational analysis linking beginning-of-treatment to posttreatment changes in neural activity to exposure to treatment components and cocaine use outcomes. In addition, only a subset of RCT participants participated in the optional fMRI component of the RCT. This limitation is mitigated by matching of groups on important baseline variables in the RCT and fMRI samples. Although the RCT included a full-factorial design, fMRI subgroup sample sizes prohibited analysis of CM \times Disulfiram or Sex/Gender \times Treatment Type interactions. Future research is needed because disulfiram may less effectively treat cocaine use in women than men (DeVito, Babuscio, Nich, Ball, & Carroll, 2014), and cognitive-control-related neural activity may differentially relate to treatment outcomes across sex/gender (Luo et al., 2013). The current study focused on cognitive-control-related brain function and was therefore only sensitive to treatment-related changes associated with this construct. Future research should investigate the relationship between treatment components and non-cognitive-control-related mechanisms, using tasks tapping other cognitive constructs with relevance to SUDs (e.g., reward sensitivity, craving). As with all treatment trials, it is not possible to control for all potential sources of variance and other measures (e.g., motivation, self-efficacy, social factors) that may fluctuate across treatment and that may also theoretically impact changes in fMRI Stroop effects. Although inclusion of a healthy control test-retest group would allow for some control of time and practice effects, these effects cannot be presumed to be identical between SUD and healthy samples for reasons discussed in the Introduction and Discussion.

Conclusions

This study is the first to assess indicators of treatment process and exposure in relation to changes in fMRI during treatment for

CUD. It represents an important, albeit preliminary, step in understanding neurocognitive mechanisms of action for well-established treatments for CUD, particularly CM. Specifically, enhanced cognitive control may be an important treatment target for SUD treatments, as indicated by the relationships seen here between exposure to components of effective therapies (CM and CBT), and posttreatment versus beginning-of-treatment changes in areas related to cognitive control as assessed by Stroop. Our approach to these analyses may also prove a step forward in utilizing fMRI to understand how empirically validated therapies may exert their effects. That is, we attempted to go beyond analyses of whether specific patterns of neural activity are associated with posttreatment drug use outcomes, which have yielded inconsistent findings across studies and have limited ability to parse out effects of specific treatment, time, or chronic or acute effects of drug use on those relationships. Rather, in these analyses, we linked changes in neural activity associated with cognitive control to putative indicators of treatment exposure for three specific treatment conditions, while separately assessing associations with drug use during the trial. This approach, which focuses on comparing effects of multiple treatments with known efficacy, reliable indicators of treatment exposure, and a well-established cognitive task (Stroop) associated with a likely common mechanism of treatment response in addicted populations may be a path toward understanding how effective therapies affect complex conditions such as SUDs.

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