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Short Communication

fMRI Stroop and behavioral treatment for cocaine-dependence: Preliminary findings in methadone-maintained individuals

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HIGHLIGHTS

- Methadone-maintained, cocaine-dependent individuals in behavioral treatment RCT
- fMRI Stroop (cognitive control task) collected at beginning-of- and post-treatment
- Baseline Stroop-related activity correlated positively with methadone dose.
- Stroop-related activity was reduced at post- versus beginning-of-treatment.
- Reduction in Stroop-related activity correlated with within-treatment abstinence.

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ABSTRACT

Background: Although behavioral treatment for cocaine use disorders is common, the use of cognitive neuroscience methods to investigate these treatments' mechanisms of action remains limited. Cognitive control (e.g., as measured by the Stroop task) has been proposed to be central to cocaine-use disorders, including treatment response.

Methods: Participants were methadone-maintained, cocaine-dependent individuals who were participating in a randomized clinical trial (RCT) of 8 weeks of treatment for cocaine-use disorder and randomized to outpatient treatment as usual (TAU) or computer-based cognitive-behavioral therapy (CBT4CBT) plus TAU. Participants completed fMRI Color-Word Stroop task at beginning-of-treatment ($N = 19$) and post-treatment ($N = 10$). Analyses assessed correlations between beginning-of-treatment Stroop effect with methadone dose or within-treatment cocaine abstinence, change in Stroop-effect at post- versus beginning-of-treatment, and correlations between 'change in Stroop effect' with methadone dose or within-treatment cocaine abstinence.

Results: Higher methadone dose was associated with higher beginning-of-treatment Stroop-related activity in the declive, culmen, and lingual gyrus. Stroop-related activity was reduced at post-treatment relative to beginning-of-treatment in the medial frontal gyrus/cingulate gyrus and thalamus/midbrain/culmen. Greater reduction in Stroop-related activity was associated with better within-treatment abstinence.

Conclusions: Diminished Stroop-related activity following treatment may be consistent with improved efficiency of cognitive-control-related activity. Although preliminary, this study is the first to demonstrate a relationship between better treatment outcomes (lower cocaine use during treatment) and greater reduction in Stroop-related activity at post- versus beginning-of-treatment in cocaine users. These findings extend prior work.

1. Introduction

Despite almost universal use of behavioral treatments for cocaine-use disorders and research spanning decades on their mechanisms of action, application of cognitive neuroscience methods to address these mechanisms remains limited (Kazdin, 2007; Morgenstern, Naqvi, Debellis, & Breiter, 2013). One approach to this question uses functional magnetic resonance imaging (fMRI) tasks measuring cognitive

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constructs with hypothesized relevance to addiction or treatment response. This enables assessment of how task-related functional activity changes with treatment or relates to abstinence outcomes. Cognitive control may be central to cocaine-use disorders (Garavan & Hester, 2007) and achievement of abstinence (Garavan, Brennan, Hester, & Whelan, 2013). The Color-Word Stroop (MacLeod, 1991) is one cognitive control task that taps response inhibition and selective attention processes- constructs implicated in addiction vulnerability, development, and maintenance (Bechara, 2005; Everitt & Robbins, 2005; Field & Cox, 2008; Jentsch & Taylor, 1999; Kober, DeVito, DeLeone, Carroll, & Potenza, 2014; Moeller et al., 2001; Torregrossa, Corlett, & Taylor, 2011; Volkow, Fowler, Wang, & Goldstein, 2002). Poor Color-Word Stroop behavioral performance has been associated with worse treatment adherence (Fagan et al., 2015) and cocaine use, and performance has improved across treatment (Nuijten, Blanken, Van den Brink, Goudriaan, & Hendriks, 2016). In cocaine users, fMRI Stroop measures differ from healthy controls (Mayer, Wilcox, Teshiba, Ling, & Yang, 2013; Mitchell et al., 2013; Moeller et al., 2014), are associated with within-treatment cocaine abstinence (Brewer, Worhunsky, Carroll, Rounsaville, & Potenza, 2008; Mitchell et al., 2013), and change across treatment (DeVito et al., 2012, 2017). Cognitive-control may be particularly relevant to cognitive-behavioral therapy (CBT), which targets cognitive-control-related processes with skills training (Carroll, 1998).

Prior studies used fMRI and Color-Word Stroop to measure cognitive-control-related activity in the context of behavioral treatment for substance-use disorders. Studies in different substance-dependent populations (cocaine, cannabis, tobacco) employing different treatments generally found higher pre-treatment Stroop-related activity associated with better abstinence outcomes (Brewer et al., 2008; Kober et al., 2014; Krishnan-Sarin et al., 2013). In two prior studies, we assessed pre- to post-treatment changes in fMRI color-word Stroop-related activity in substance users. In a mixed substance-dependent sample ($N = 12$) randomized to computer-based training for CBT (CBT4CBT) or treatment as usual (TAU), Stroop-related activity was reduced at post-treatment versus pre-treatment in regions implicated in cognitive-control, including the thalamus/subthalamic nucleus/midbrain, middle/superior temporal gyrus, IFG/caudate, cuneus, anterior cingulate gyrus, middle frontal gyrus and superior frontal gyrus (DeVito et al., 2012). These changes were interpreted as consistent with improved cognitive-control-related neural efficiency following treatment. Similarly, we found, in cocaine-dependent individuals ($N = 35$) randomized to TAU with or without CBT, contingency management and/or disulfiram, Stroop-related activity was reduced at post- versus beginning-of-treatment in the hippocampus, thalamus, cingulate, postcentral and precentral gyri, precuneus and culmen. Furthermore, greater reductions in Stroop-related activity were associated with more CBT engagement and contingency-management prizes, but not with disulfiram-related measures (DeVito et al., 2017). However, changes in neural activity from pre- to post-treatment have not yet been associated with drug use outcomes.

The current study extends prior research, in an independent randomized controlled trial (RCT) sample. Individuals seeking treatment for current primary cocaine dependence, who were already stabilized on methadone (for opioid dependence), were randomized to CBT4CBT or TAU within an outpatient methadone-maintenance-treatment setting. We assessed associations between beginning-of-treatment fMRI Stroop-related activity ($N = 19$) with substance-use history, methadone dose, and within-treatment cocaine-abstinence. Within participants who also completed the fMRI Stroop task at the end of the 8-week treatment ($N = 10$), we assessed changes in Stroop-related activity at post-treatment versus beginning-of-treatment, and correlations between within-treatment cocaine abstinence or methadone dose with 'changes in Stroop-related activity'. We hypothesized that greater Stroop-related activity at beginning-of-treatment would be associated with better abstinence outcomes, and participants would show reduced Stroop-related activity at post-treatment versus pre-treatment in regions involved in cognitive-control and that reductions in Stroop-related activity would be associated with better cocaine-use outcomes.

2. Methods

2.1. Participants

Treatment-seeking participants were recruited to the fMRI study prior to randomization to treatment for cocaine dependence (Carroll et al., 2014). Participants met DSM-IV criteria for current cocaine dependence (past 30 days, per SCID interviews), were on a stable dose of methadone for at least 2 months (to manage opioid use disorder), aged ≥18 years, spoke English, read at ≥6th grade level, and had no current unstabilized psychotic disorder, suicidal or homicidal ideation, claustrophobia, colorblindness, history of severe head trauma with loss of consciousness, or MRI-contraindicated metallic implants. Although 101 RCT participants were randomized to a treatment condition, and 93 started treatment, only a small proportion participated in the optional fMRI study component. The fMRI study began after the RCT had already begun. Once the fMRI study began, all RCT participants were invited to participate in the fMRI component. Unwillingness or inability (due to scheduling or fMRI safety eligibility criteria) to participate in the fMRI component did not affect their RCT eligibility. A subset of fMRI analyses included all participants who initiated treatment and provided usable fMRI Stroop data at beginning-of-treatment ($N = 19$); other analyses were restricted to participants who had fMRI Stroop data from both beginning-of-treatment and post-treatment ($N = 10$) (see Section 2.4 for details). Participants provided written informed consent approved by the Yale School of Medicine IRB prior to participation.

2.2. Treatment

RCT methods are reported in full elsewhere (Carroll et al., 2014). Briefly, participants were randomized to standard outpatient methadone-maintenance treatment as usual (TAU), or TAU plus weekly access to CBT4CBT, for the 8-week treatment protocol. TAU included daily methadone maintenance and weekly group-therapy sessions, provided by the clinic. Research assistants monitored clinical symptoms and collected study urine toxicology screens and self-reports of recent substance use at twice-weekly visits.

2.3. Clinical assessments

Day-by-day self-reported use of drugs was collected weekly using Timeline Follow back method (Robinson, Sobell, Sobell, & Leo, 2014). Primary RCT outcomes were percent days self-reported abstinence, longest duration of self-reported abstinence, and percent cocaine-negative urines. Briefly, within the full RCT sample, the CBT4CBT group had better treatment outcomes and displayed continued improvement over follow-up (Carroll et al., 2014). Primary clinical outcomes for fMRI analyses were those used in RCT, except a continuous, instead of dichotomous, measure for longest duration of continuous abstinence was used, since the data distribution was not suitable for this subsample.

2.4. fMRI methods

Participants were administered the event-related fMRI Stroop color-word interference task, a measure of cognitive-control (DeVito et al., 2012; Kober et al., 2014), on two occasions: at beginning-of-treatment and following the 8-week treatment (for task, preprocessing, and first-level analysis details, see Supplemental materials).

Briefly, fMRI analyses were conducted in NeuroElf v0.9 (NeuroElf.net) implemented in MATLAB 7.3 (Mathworks, Natick, MA). First-level analyses used robust regression within a GLM approach with motion and high-pass filter parameters as regressors of no interest (DeVito et al., 2017;Kober et al., 2014;Kober, Brewer, Height, & Sinha, 2017).

For second-level random-effects analyses, primary contrasts were the 'Stroop effect' (Incongruent trials > Congruent trials) at beginning-of-treatment and post-treatment, and 'change in Stroop effect' (Stroop $Effect_{POST}$-Stroop $Effect_{BEGINNING\text{-}OF\text{-}TREATMENT}$).

First, correlations were computed between beginning-of-treatment 'Stroop-effect' and methadone dose and measures of within-treatment cocaine abstinence ($N = 19$). Second, *t*-tests compared 'Stroop-effect' contrasts at post-treatment versus beginning-of-treatment ($N = 10$). Third, correlations were performed between the 'change-in-Stroop-effect' contrast and methadone dose or within-treatment cocaine abstinence. Finally, to assess potential confounds, analyses tested whether baseline fMRI Stroop differed by treatment group or correlated with substance-use history, and found no significant effects (Supplemental Materials). All analyses were whole-brain- and familywise-error-corrected, two-tailed $p_{FWE} < 0.05$. For correlations, non-parametric rank-order correlations were used if variables did not meet parametric assumptions.

3. Results

The sample ($N = 19$) was predominantly Caucasian (63%), female (74%), and (average (SD)) 41.7 (9.6) years old, having 11.8 (7.7) years of lifetime cocaine use, 13.2 (10.0) days of cocaine use in month prior to treatment, and methadone dosed 80.0 (31.8) mg/day. For more details on demographics, clinical characteristics, treatment engagement and drug use outcomes see Supplemental Table 1. Out of scanner Stroop data indicated the expected 'Stroop effect' (i.e., slower response time to incongruent versus congruent trials) and a non-significant trend towards improved performance at post-treatment relative to baseline (trend fewer errors without significant change in response times; for details, see Supplemental materials).

First, methadone dose was positively associated with Stroop-related activity (greater difference between congruent and incongruent trials) in the declive, culmen and lingual gyrus (Table 1A; Supplemental Fig. 1). There were no significant correlations between beginning-of-treatment Stroop effect and within-treatment cocaine abstinence. Second, Stroop-effect-related activity was significant reduced post-treatment versus beginning-of-treatment in the medial frontal gyrus (extending into mid-cingulate cortex), and thalamus (extending into midbrain and culmen) (Table 1B, Fig. 1A, Supplemental Fig. 2). Third, 'change-in-Stroop-effect' was associated with within-treatment cocaine abstinence (Table 1C, Fig. 1B, Supplemental Fig. 3). Longer duration of abstinence was associated with lower Stroop-related activity at post-treatment relative to beginning-of-treatment in the postcentral gyrus (extending into precentral gyrus, inferior parietal lobule and cingulate gyrus), bilateral insula, and superior temporal gyrus. Similarly, percent days self-reported abstinence was inversely correlated with 'change-in-Stroop' in middle temporal gyrus, extending into superior temporal gyrus, postcentral gyrus, and posterior insula. No significant associations were found between methadone dose or drug-negative urines and 'change-in-Stroop-effect'.

Table 1
fMRI Stroop results.

Regions of activation	R/L	Peak coordinates			k	Statistics (*t*-value)	
		x	y	z		Maximum Voxel	Cluster Mean
A. Correlation between clinical measures and beginning-of-treatment Stroop effect							
Methadone dose at pre-treatment baseline							
Culmen	L	−24	−39	−30	348	0.82	0.65
Declive	R	12	−93	−27	145	0.78	0.63
Lingual Gyrus	L	0	−87	−18	88	0.76	0.63
B. Change in fMRI Stroop effect at post-treatment vs. beginning-of-treatment							
Medial Frontal Gyrus/ Cingulate Gyrus	L	−9	15	48	102	−7.92	−3.99
Thalamus/ Midbrain/ Culmen	R	6	−12	−9	161	−7.21	−4.08
C. Correlations between clinical measures and change in fMRI Stroop effect							
Longest duration of continuous abstinence during treatment							
Postcentral Gyrus/ Precentral Gyrus/IPL/ Cingulate Gyrus	L	−18	−27	63	911	−0.98	−0.84
Insula	R	39	−24	15	366	−0.98	−0.83
Insula	L	−42	−36	27	199	−0.97	−0.84
Superior temporal gyrus	L	−57	12	−21	154	−0.96	−0.84
Percent days cocaine abstinence during treatment							
Middle Temporal Gyrus/ Superior Temporal Gyrus/ Postcentral Gyrus/Insula	L	−60	−39	3	200	−0.97	−0.82

All results presented survive family wise error correction for multiple comparisons at the whole brain level to two-tailed $p_{FWE} < 0.05$.
Abbreviations: R = right, L = left, k = cluster size (in voxels).
A. Whole-brain correlation between the Stroop Effect (Incongruent > Congruent) contrast at beginning of treatment within the full sample of with available fMRI and clinical data (N = 19). The remaining clinical measures tested did not show significant correlation with beginning of treatment Stroop effect: days of cocaine use in month prior to treatment; years of cocaine, herion, marijuana or alcohol use; longest duration of cocaine abstinence during treatment, percent days cocaine abstinence during treatment, percent cocaine negative urines during actual treatment.
B. Stroop Effect at post-treatment versus beginning of treatment ($(Incongruent_{POST}$-$Congruent_{POST})$ -$(Incongruent_{BEGINNNING}$-$Congruent_{BEGINNING})$ within the full sample of with available data at both time points (N = 10; 4 CBT4CBT, 6 TAU).
C. Whole-brain correlation between Change-in-Stroop-Effect contrast and cocaine-use treatment outcomes, within the full sample with available data at beginning of treatment and post-treatment ($N = 10$). The remaining cocaine-use outcome measure tested (percent cocaine negative urines during treatment) did not show a significant correlation with Change-in-Stroop effect.

4. Discussion

4.1. Main findings

Within methadone-maintained cocaine-dependent participants, methadone dose correlated positively with Stroop-effect-related neural activity at beginning-of-treatment. Stroop-related activity was reduced at post- versus beginning-of-treatment. Greater reduction in Stroop-related activity was associated with more within-treatment abstinence.

4.2. Consistency with prior research

Prior studies in marijuana users, a mixed substance-use-disorder sample, and adolescent cigarette smokers, generally found that greater Stroop-related activity at pre-treatment was associated with 'better' abstinence outcomes within treatment (Brewer et al., 2008; Kober et al., 2014; Krishnan-Sarin et al., 2013); however, the current analysis in methadone-maintained cocaine users found no significant correlations between beginning-of-treatment Stroop effect and subsequent within-treatment cocaine abstinence. Current methadone status or history of opioid dependence may impact associations between pre-treatment fMRI and abstinence outcomes. For example, a prior study associated lower pre-treatment reward-anticipation-related caudate activity with greater abstinence in methadone-maintained cocaine users, but not within non-methadone-maintained cocaine users (Yip et al., 2016).

The finding of reduced Stroop-related activity at post- versus beginning-of-treatment in regions implicated in cognitive-control is

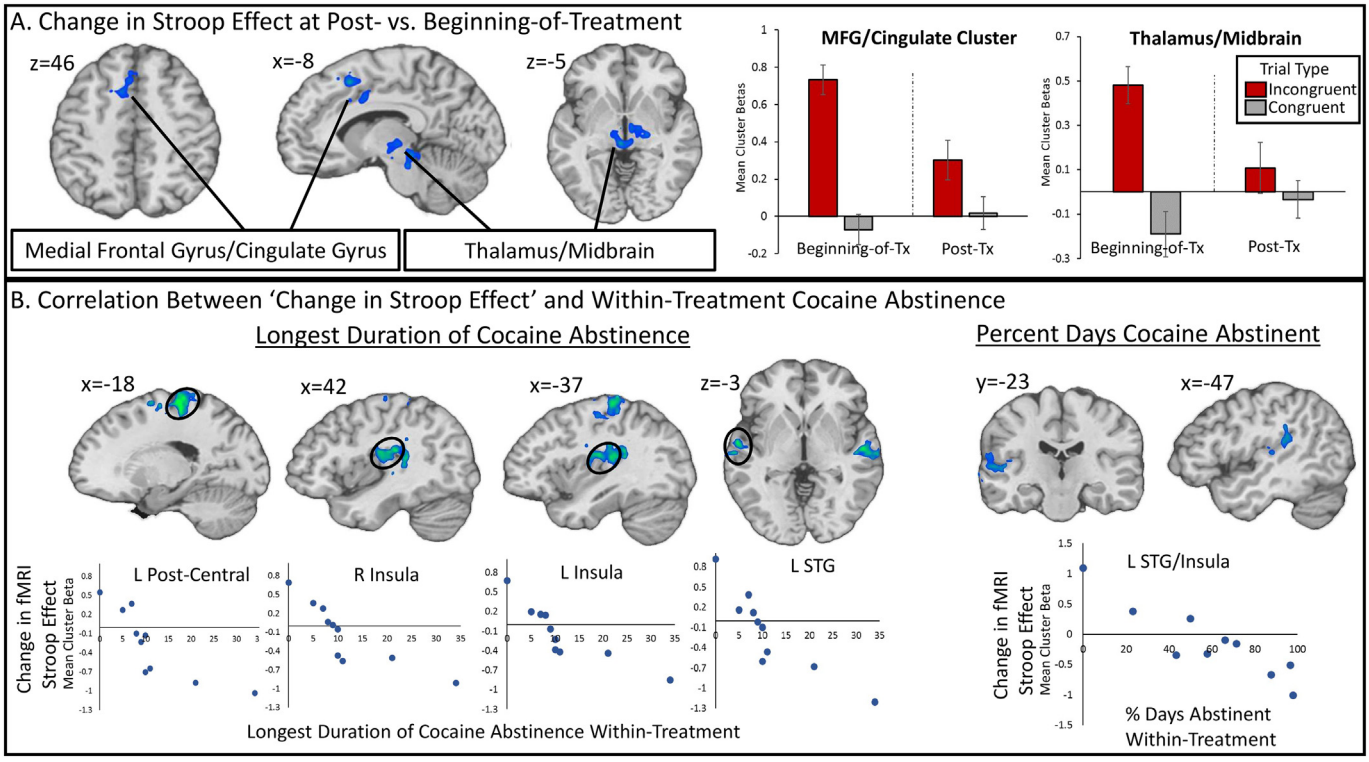

Fig. 1. Change in Stroop effect at post-treatment vs. beginning-of-treatment, and correlation with within-treatment abstinence.
A. Stroop Effect contrast at post-treatment versus beginning-of-treatment ((Incongruent$_{POST}$ > Congruent$_{POST}$) > (Incongruent$_{BEGINNING}$ > Congruent$_{BEGINNING}$)) within the full sample of with available data at both time points (N = 10; 4 CBT4CBT, 6 TAU). All results presented survive family wise error correction for multiple comparisons at the whole brain level to two-tailed $p_{FWE} < 0.05$. See results in Table 2B. Blue indicates regions where Stroop-effect-related activity is lower at post-treatment relative to beginning-of-treatment. Bar graphs show the extracted average betas from these clusters at beginning-of-treatment and post-treatment for incongruent trials (red) and congruent trials (gray) by beginning-of-treatment (left bars) and post-treatment (right bars) separately within significantly change clusters within MFG/Cingulate and Thalamus/Midbrain. Abbreviations: MFG = Medial Frontal Gyrus; Tx = Treatment.
B. Whole brain correlation between 'Change in Stroop Effect' at post-treatment versus beginning of treatment, and cocaine abstinence during treatment within the full sample with available data (N = 10). All results presented survive family wise error correction for multiple comparisons at the whole brain level to two-tailed $p_{FWE} < 0.05$. Blue indicates an inverse relationship showing better abstinence outcomes associated with greater reduction in Stroop Effect at post-treatment relative to beginning-of-treatment. Scatterplots show the extracted betas from each significant cluster (as reported in Table 1C). Longest duration of continuous abstinence during treatment (days) variable did not meet parametric assumptions, therefore rank-order non-parametric correlations were used. Percent days self-reported cocaine abstinence during treatment variable met parametric assumptions, therefore robust parametric correlations were used. Abbreviations: R = right; L = left; STG = Superior Temporal Gyrus. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

broadly consistent with two prior studies: one in a mixed substance-use-disorder sample, receiving the same behavioral treatment conditions as here (TAU, CBT4CBT) but without methadone-maintenance treatment (DeVito et al., 2012), and another in a cocaine-dependent sample (without methadone) receiving TAU with or without CBT, contingency management and disulfiram (DeVito et al., 2017). The current findings show overlaps in regions implicated in change or associations with outcome from our prior work, possibly reflecting more generalizable treatment-related changes across treatment types and clinical samples, while distinctions may relate to differences in clinical samples (e.g., drug type) and treatment-specific effects (e.g., methadone maintenance). Diminished cognitive-control-related activity following treatment could be consistent with improved efficiency of cognitive-control-related activity. Importantly, this study is the first to demonstrate a relationship between better treatment outcomes (lower cocaine use during treatment) and greater reduction in Stroop-related activity at post- versus beginning-of-treatment in cocaine users. These findings extend prior work showing that greater reduction in Stroop-related activity was associated with greater engagement in well-supported, evidenced-based treatments for cocaine dependence (i.e., CBT, contingency management;DeVito et al., 2017).

Prior fMRI studies of cognitive-control tasks have shown that acute cocaine administration and abstinence could both alter cognitive-control-related activity (Connolly, Foxe, Nierenberg, Shpaner, & Garavan, 2012; Garavan, Kaufman, & Hester, 2008). Therefore, correlations between within-treatment abstinence and 'change-in-Stroop-effect' across treatment may reflect abstinence-related changes. However, the observation that these changes (across treatment overall, and correlations with abstinence) are observed in separable clusters could suggest that both treatment and abstinence may each have independent effects on cognitive-control-related processes. This could not be directly tested within our study.

The positive correlation between methadone dose and Stroop-related activity at beginning-of-treatment could be consistent with less efficient cognitive-control-related processes and/or greater compensatory activity in individuals receiving higher methadone doses. Prior studies have found cognitive impairments in methadone-maintained individuals, including on the Stroop (Mintzer & Stitzer, 2002). Specifically, individuals with higher methadone doses exhibit worse cognitive performance, including on tasks of vigilance and memory (Curran, Kleckham, Bearn, Strang, & Wanigaratne, 2001; Loeber, Kniest, Diehl, Mann, & Croissant, 2008). Furthermore, an fMRI study using the Monetary Incentive Delay Task found inverse correlations between methadone doses at pre-treatment and anticipation of reward or loss in methadone-maintained cocaine users (Yip et al., 2016).

4.3. Limitations and considerations

Due to the small sample, findings should be considered preliminary. It was not possible to assess how treatment components contribute to neural change, since treatment exposure indicators differed by treatment group and within-treatment-group sample size was insufficient for analysis of differential change in Stroop-related activity by treatment condition. Overall change likely represents changes common across conditions, which may be attributable to generalizable treatment effects as well as non-treatment-related (e.g., test-retest) effects. Furthermore, clinically-representative RCT samples introduce more variability than is typical of many other fMRI studies, but substantially improve clinical generalizability. Since both the self-reported, but not the urine-based, abstinence measure significantly correlated with 'change in Stroop', potential sources for this inconsistency were considered. See Supplemental Materials for clarification that a) all three abstinence measures were strongly, but not perfectly, intercorrelated; b) measures were capturing slightly different abstinence constructs, thereby justifying the use of multiple outcome measures; and c) correlations between urine abstinence and 'change in Stroop' were consistent with the self-report findings, but did not survive the statistical threshold. The absence of Stroop accuracy data in the scanner prohibited restriction of the analysis to correct responses or consideration of the possible contribution of error processing (see Supplemental Materials). This confirmatory study's limitations should be considered in balance with the dearth of research on neural mechanisms of behavioral treatments for substance abuse (e.g., Morgenstern et al., 2013).

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Contributors

Drs. Potenza and Carroll designed the study (neuroimaging component: Dr. Potenza; RCT: Dr. Carroll). Dr. DeVito planned and performed the analyses and wrote the manuscript. Dr. Kober consulted on the fMRI analyses. All authors contributed to the interpretation of results, provided edits to the manuscript and approved the final version of the manuscript.

Conflict of Interest

Drs. DeVito and Kober report no competing interests. Dr. Potenza has consulted for Lundbeck, Ironwood, Shire, and INSYS pharmaceuticals and RiverMend Health and has received research support from Pfizer Pharmaceuticals. Dr. Carroll is a member of CBT4CBT LLC, which makes CBT4CBT, a computer-based version of cognitive behavioral therapy, available to qualified clinical providers and organizations on a commercial basis. Dr. Carroll works with Yale University to manage any potential conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.addbeh.2018.09.005.

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