

Performance on the Stroop Predicts Treatment Compliance in Cocaine-Dependent Individuals

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Treatment dropout is a problem of great prevalence and stands as an obstacle to recovery in cocaine-dependent (CD) individuals. Treatment attrition in CD individuals may result from impairments in cognitive control, which can be reliably measured by the Stroop color–word interference task. The present analyses contrasted baseline performance on the color-naming, word-reading, and interference subtests of the Stroop task in CD subjects who completed a cocaine treatment trial (completers: $N = 50$) and those who dropped out of the trial before completion (non-completers: $N = 24$). A logistic regression analysis was used to predict trial completion using three models with the following variables: the Stroop task subscale scores (Stroop model); the Hamilton depression rating scale (HDRS) scores (HDRS model); and both the Stroop task subscale scores and HDRS scores (Stroop and HDRS model). Each model was able to significantly predict group membership (completers vs non-completers) better than a model based on a simple constant (HDRS model $p = 0.02$, Stroop model $p = 0.006$, and Stroop and HDRS model $p = 0.003$). Models using the Stroop preformed better than the HDRS model. These findings suggest that the Stroop task can be used to identify cocaine-dependent subjects at risk for treatment dropout. The Stroop task is a widely available, reliable, and valid instrument that can be easily employed to identify and tailor interventions of at risk individuals in the hope of improving treatment compliance.

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INTRODUCTION

Dropout from substance abuse treatment in general and cocaine dependence treatment in particular is a serious problem, resulting in reduced treatment efficacy, increased likelihood of relapse, increased medical illness, and social problems related to substance abuse (Alterman *et al*, 1996; Mulvaney *et al*, 1999). Conversely, the number of months in treatment for cocaine dependence is associated with decreased cocaine use, improved outcome, and decreased morbidity (Hser *et al*, 2006). Attrition in cocaine treatment trials is a problem across treatment modalities. Pharmacologic treatment trials for cocaine dependence report dropout rates of 0–84% (de Lima *et al*, 2004). Psychotherapy treatment trials for cocaine dependence report dropout rates of 29–41% (Kang *et al*, 1991; Simpson *et al*, 1999).

Trials that combine pharmacologic treatments with psychotherapy report dropout rates of 30–40% (Carroll *et al*, 1994; Elkashef *et al*, 2005). Variables related to treatment dropout include a number of demographic and socioeconomic factors such as low education, African-American ethnicity, female gender, reporting cocaine as the drug of choice, younger age of subjects, current unemployment, high level of cocaine use during the lead-in period, history of arrests, longer drug use histories, abstinence symptoms, and previous treatment enrollment (Alterman *et al*, 1996; Siqueland *et al*, 1998; Mulvaney *et al*, 1999; King and Canada, 2004; Bisaga *et al*, 2005).

Cognitive testing has also been used to predict attrition in drug abuse treatment programs (Simpson *et al*, 1997; Teichner *et al*, 2002; Aharonovich *et al*, 2003, 2006). In a cocaine treatment study utilizing cognitive behavioral therapy (CBT) plus a trial of gabapentin or placebo, performance on computerized tests across most cognitive domains was poorer in dropouts relative to completers, independent of pharmacologic status (Aharonovich *et al*, 2006). This suggests that identification of deficits on cognitive tasks may be a means of identifying subjects at risk for dropout.

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Cognitive control allows the inhibition of a habitual or prepotent response such as drug use and non-compliance with treatment in favor of a more appropriate response such as abstaining from drug use or engaging in treatment. The Stroop Color Word Task is considered to be one of the most reliable and widely used psychometric tests of cognitive control (Stroop, 1935; MacLeod, 1991). For this reason it may be an ideal instrument to screen for individuals at risk for treatment dropout, due to their hypothesized inability to inhibit a prepotent response. The original Stroop task is comprised of three subtests, designed to assess the subject's ability to suppress interfering stimuli. In the color-naming subtest, the subject is asked to report the color of randomly sequenced color rectangles, establishing the tendency to respond to color. In the word-reading subtest, the subject is asked to read color words randomly printed in black ink, establishing a response set to reading color words. In the interference subtest, the subject is given color words, which are printed in an incongruent ink color (eg the word 'red' printed in blue ink). The subject is asked to report the ink color, and therefore has to suppress the tendency to read the color word. There is a strong prepotent tendency to read the presented text of a color word rather than naming the color in which the word is printed.

The Stroop task is believed to test key cognitive processes associated with selective attention, cognitive control, and goal-oriented behavior that supports the ability to select a weaker, task-relevant response in the face of competition from a potentially stronger, task-irrelevant one (Pardo *et al*, 1990; MacDonald *et al*, 2000). Difficulty with inhibitory processing is reflected by an increase in time in the interference subtest relative to the color-naming or word-reading subtests. Slowed performance on the interference subtest has been interpreted to reflect difficulty in resisting interference, an inhibitory function associated with frontal cortical integrity (Mesulam, 1985). Subjects with prefrontal impairment have difficulty with this task (Golden, 1976), suggesting that frontally mediated processes are involved in adhering to the goals or rules of the task in the face of a competing, stronger (ie more salient, habitual, or prepotent) response.

The present study assessed whether performance on the Comalli version of the Stroop task (Comalli *et al*, 1962) was able to predict treatment attrition in cocaine-dependent subjects. It was hypothesized that dropouts would exhibit poorer performance scores on the interference subtest than subjects who completed the course of treatment, suggesting that impairment in the ability to inhibit a prepotent response is a marker for poor treatment compliance.

MATERIALS AND METHODS

Study Design

The National Institute on Drug Abuse (NIDA) has developed and implemented a series of treatment trials to evaluate a number of pharmacologic agents as potential treatments for cocaine dependence (Liederman *et al*, 2000, 2005; Berger *et al*, 2005; Ciraulo *et al*, 2005; Elkashef *et al*, 2005; Winhusen *et al*, 2005). Boston University School of Medicine was the site of three NIDA-sponsored cocaine dependence treatment trials that were similar in design.

All studies included a CBT platform of weekly individual sessions that were based on a CBT manual developed for cocaine dependence. The trial name, pharmacologic treatments, and length of treatment were as follows: Trial 1, venlafaxine, pramipexole, and placebo, 12 weeks; Trial 2, reserpine and placebo, 12 weeks; and Trial 3, tiagabine and placebo, 17 weeks. As a supplement to the pharmacologic treatment trials, all cocaine-dependent subjects completed imaging studies before randomization and at maximal treatment (weeks 12, 12, and 17). Cocaine-dependent subjects underwent neuropsychological testing concurrent with the first scanning session. The results of the imaging studies have been reported elsewhere (Ke *et al*, 2004; Streeter *et al*, 2005, 2006). The entrance criteria for the cocaine-dependent subjects were similar in all three studies, allowing comparison across studies. In order to come to the final assessment of the imaging study, subjects had to have completed the clinical trial. Subjects who missed more than two consecutive weeks of treatment were withdrawn from the study, as those on medications would have run out of medication after 2 weeks.

Inclusion/Exclusion Criteria

All subjects signed informed consent forms that were approved at the appropriate Institutional Review Boards of Boston Medical Center, McLean Hospital, and the Boston VA Healthcare System. Eligible subjects were cocaine-dependent persons between 18 and 60 years of age enrolled in an NIDA-sponsored treatment study. All cocaine-dependent subjects met the Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition (DSM-IV) diagnosis of cocaine dependence and reported using cocaine on at least 2–6 occasions within the 28-day period before screening (American Psychiatric Association, 1994). Self-report of current cocaine use was substantiated with 1–3 urine specimens that were positive for the cocaine metabolites over a two-week period before study entry. Women with childbearing capacity were required to use an acceptable method of birth control. Potential subjects were excluded if they had a current dependence on any psychoactive drug other than cocaine, alcohol, or nicotine. In addition, those with neurological or psychiatric disorders requiring immediate treatment or that would have made medication compliance difficult were excluded. Other reasons for exclusion included serious medical illness, current prescription drug treatment, asthma, amenorrhea due to pregnancy, abnormal laboratory results during screening, or contraindication to magnetic resonance scanning. Cocaine-dependent subjects with a current history of alcohol dependence not requiring medical detoxification were accepted.

Due to the high incidence of co-morbidity of cocaine and alcohol dependence in the cocaine-dependent sample population, the following characteristics resulted in exclusion: liver function tests including a gamma-glutamyl transferase greater than three times normal, a history of a complicated alcohol withdrawal such as delirium tremens or seizures, or the need for a medical detoxification. All subject evaluations were reviewed by a psychiatrist with additional qualifications in addictions and many years of experience in

treating individuals with comorbid alcohol and drug dependence (OS).

Neuropsychological Battery and Other Assessment Instruments

The neuropsychological test battery was administered by trained psychometricians under the supervision of a neuropsychologist (DYT) at baseline before randomization. Only the results from the Stroop task administered using the Comalli–Kaplan Version that allows for self-correction of errors before moving to the next stimuli are discussed in this paper (Comalli *et al*, 1962). This version of the Stroop task includes the three subtest conditions previously discussed, which are contained on three stimulus cards sets, each containing 100 stimuli. The order of administration is invariable, and is color naming, followed by word reading, and finally interference. All sections are timed, and both time to complete each condition and errors made are recorded as dependent variables. The results from the larger study analyzing performance on other baseline neuropsychological tasks will be discussed elsewhere.

All subjects were evaluated using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID): Patient Edition (First *et al*, 1995) and the Addiction Severity Index (ASI) (McLellan *et al*, 1992) before randomization. Psychiatric diagnoses were made according to SCID criteria. Measures of alcohol and substance abuse were taken from the ASI, and depression was evaluated using the Hamilton depression rating scale (HDRS) (Hamilton, 1967).

Urine toxicology was obtained three times a week for quantitative analysis of the cocaine metabolite benzoylecgonine (BE). The Preston criteria were used to determine new use (Preston *et al*, 1997). The Triage[®] Drugs of Abuse Panel (Biosite[®]) was used to test urine samples for the following drugs of abuse: cocaine, tetrahydrocannabinoids, amphetamines, benzodiazepines, and opiates. Average baseline (urine samples collected before the first scan) and total urine (all available urine samples) BE levels were computed by summing the logarithmically transformed urine BE levels and dividing by the number of available baseline data points or total number of data points, respectively.

Statistical Analyses

Categorical data were analyzed using χ^2 -tests and continuous and ordinal data were analyzed using between-groups one-way and factorial ANOVAs. Non-parametric statistics (eg Kruskal–Wallis and Fisher's exact tests) were used when the respective data set violated assumptions of distribution normality or homogeneity of variance. Analyses of covariance (ANCOVA) were used to control for covariates of *a priori* theoretical interest. Correlational analyses used Pearson's product-moment correlations and the series of direct logistic regression analyses used the 'forced entry' method. Group membership (ie completers and non-completers) was determined by dichotomizing the predicted log odds of success for the fitted models, assigning subjects to the predicted completer group if the predicted log odds was greater than zero (ie a predicted probability of completion greater than 50%). Statistical significance

required two-tailed $p < 0.05$. Analyses employed the commercial statistical analysis systems SAS Version 8.2, STATA 8.2, and SPSS Version 13.0. The primary analyses examined the ability of Stroop task scores to discriminate between completers and non-completers. The secondary analyses explored the effect of urine metabolites for cocaine and other substances of abuse on Stroop task performance.

RESULTS

Subject Acquisition

Treatment-seeking cocaine-dependent individuals already enrolled in a treatment study underwent a screening interview at Boston Medical Center, at which time informed consent was obtained for this study. Subjects were considered enrolled in the study when they arrived for the neuropsychological testing at McLean Hospital. Subjects were categorized as completers: subjects who had neuropsychological testing at baseline and returned for the final assessment at McLean Hospital; or non-completers: subjects who had neuropsychological testing at baseline but did not return for the final assessment at McLean Hospital. In Trials 1, 2, and 3, there were 38, 19, and 17 enrolled subjects who participated in the baseline neuropsychological testing; of these, 7, 6, and 11 did not complete the respective trial, resulting in 50 completers and 24 non-completers. The percentage attendance in the three times a week assessments were $90.2 \pm 10.1\%$ for the completers and $47.3 \pm 27.5\%$ for the non-completers ($N = 20$). There were four non-completers that did not attend any assessments after the neuropsychological testing. There were 11 completers from Trial 1 who also participated in Trial 2, three of whom participated in Trial 3, and one completer from Trial 2 who also participated in Trial 3. To avoid test-retest artifacts, only the first baseline neuropsychological data were considered for subjects who participated in more than one trial (Table 1).

Demographics

The completers and non-completers did not differ with respect to any of the measured demographic variables including age, gender distributions, years of education, ethnicity, cocaine use in the preceding 30 days, number of years of cocaine use, and current or past alcohol abuse/dependence. However, the two groups did exhibit differential patterns of treatment assignment (placebo, medication, and non-randomized), owing to primarily the number of non-randomized subjects in the cohort of non-comple-

Table 1 Distribution of Completers and Non-Completers (Count and Percentage of Total) by Source Study

	Study			
	Trial 1	Trial 2	Trial 3	Total
Completed session 1	38	19	17	74
Non-completers (%)	7 (18)	6 (32)	11 (65)	24 (32)
Completers (%)	31 (82)	13 (68)	6 (35)	50 (68)

Table 2 Demographic Variables (M (SD) (%)) in Cocaine-Dependent Subjects by Trial Completion (Non-Completers (N = 24) and Completers (N = 50))

	Non-completers	Completers	F	df	p
Age	41.88 (6.19)	45.12 (8.19)	2.95	1,72	0.090
Gender (F/M)	9/15	13/37	1.03*	1	0.31
Education	12.10 (1.81) ^a	12.88 (2.26)	1.99	1,69	0.16
Ethnicity			0.30*	3	0.96
African-American (%)	20 (83)	43 (86)			
Caucasian (%)	2 (8)	4 (8)			
Hispanic (%)	1 (4)	2 (4)			
Multi-racial/other	1 (4)	1 (2)			
ASI cocaine use days	14.85 (7.80) ^b	16.98 (9.44)	0.48**	1	0.49
Years of cocaine use	14.70 (6.11) ^b	15.38 (7.78)	0.12	1,68	0.73
Current alcohol abuse/dependence (%)	8/20 (40)	13/50 (26)	1.33*	1	0.25
Past alcohol abuse/dependence (%)	2/20 (10)	17/50 (34)	4.16*	1	0.041
Ham-D	9.89 (7.99) ^c	5.38 (5.32)	4.16**	1	0.041
Ham-D > 12 (%)	7/18 (39)	5/42 (12)			0.031***
Treatment assignment (placebo/medication/not randomized)	9/9/6	21/29/0	13.91*	2	0.001
Treatment assignment (placebo/medication)	9/9	21/29	0.34*	1	0.56

*, χ^2 ; **, Kruskal–Wallis χ^2 ; ***, Fisher's exact test.

^aN = 21.

^bN = 20.

^cN = 18.

ters. In randomized subjects, the two groups did not exhibit differential treatment assignments (placebo or medication) (Table 2).

Analysis of Stroop Results

A series of ANOVAs were performed to assess performance differences on the Stroop subtests between completers and non-completers. Completers took significantly less time to finish the color-naming and interference subtests, and also yielded lower derived interference scores (interference-color naming). In addition, there was a trend toward completers taking less time on the word-reading subtest relative to non-completers. After a Bonferroni correction for multiple analyses ($\alpha = 0.01$), only color naming and interference remained significantly different between the two groups (Table 3).

There were a number of potential covariates that could have affected the Stroop results. For instance, there were trends for the completers to be older and to possess a higher incidence of past alcohol abuse or dependence. In addition, non-completers had significantly higher HDRS scores than completers and a significantly greater percentage of their members received HDRS scores greater than 12, with higher scores indicating greater depressive symptoms (Hamilton, 1967). When age, past alcohol abuse/dependence, and HDRS scores were treated as covariates, there were no changes in the main effects reported above.

Logistic Regression

A logistic regression analysis was used to predict trial completion. Three models using the following variables

Table 3 Baseline Stroop Subtest Performance Scores in Seconds (M and (SD)) in Cocaine-Dependent Subjects as a Function of Trial Completion (Non-Completers (N = 24) and Completers (N = 50))

	Non-completers	Completers	F	df	p	η_p^2
Color naming	77.63 (16.19)	66.20 (11.94)	8.48*	1	0.004	0.14
Word reading	61.08 (22.24)	51.80 (10.08)	2.87*	1	0.090	0.07
Interference	163.96 (55.80)	132.12 (30.43)	10.12	1,72	0.002	0.12
Derived interference	86.33 (47.71)	65.92 (26.12)	5.67	1,72	0.020	0.07

*, Kruskal–Wallis χ^2 .

were explored to predict completion: the Stroop task subscale scores (ie color naming, word reading, and interference) (Stroop model); the HDRS scores (HDRS model); and both the Stroop task subscale scores and HDRS scores (Stroop and HDRS model). A fourth model that is pure chance is also reported. Sensitivity (predicted completers/actual completers), specificity (predicted non-completers/actual non-completers), positive predictive value (actual completers/predicted completers), and negative predictive value (actual non-completers/predicted non-completers) are reported for each model in Table 4.

Each model was able to significantly predict group membership (completers vs non-completers) better than a model based on a simple constant (HDRS model $p = 0.02$, $df = 1$, $\chi^2 = 5.9$; Stroop model $p = 0.006$, $df = 3$, $\chi^2 = 12.6$; Stroop and HDRS model $p = 0.003$, $df = 4$, $\chi^2 = 15.9$). The HDRS model alone has good sensitivity (93%), poor specificity (28%), the lowest positive predictive value (75%),

Table 4 Logistic Regression Models with 95% Confidence Intervals

Model	Sensitivity	Specificity	Positive predictive value	Negative predictive value
<i>Stroop</i>				
Point estimates (%)	98	42	78	91
95% CI	(89, 100)	(22, 63)	(66, 87)	(59, 100)
<i>HDRS</i>				
Point estimates (%)	93	28	75	63
95% CI	(81, 99)	(10, 53)	(61, 86)	(24, 91)
<i>Stroop and HDRS</i>				
Point estimates (%)	95	50	82	82
95% CI	(84, 99)	(26, 74)	(68, 91)	(48, 98)
<i>Pure chance</i>				
Point estimates (%)	50	50	68	32
95% CI	(36, 64)	(36, 64)	(50, 82)	(18, 50)

Sample size decreases in the models using the HDRS due to a limited number of HDRS data points (ie completers $N = 42$ and non-completers $N = 18$).

and the lowest negative predictive value (62.5%). The Stroop model has the highest sensitivity (98%), a fair specificity (42%), a good positive predictive value (78%), and a very good negative predictive value (91%); observe that the Stroop model has superior performance in every category compared with the HDRS model. Compared to the Stroop model, the Stroop and HDRS model has a lower sensitivity (95%), an increased specificity (50%), and a resulting increased positive predictive value (82%) and a decreased negative predictive value (82%). The predictive value of all models is better than the pure chance approach.

Concurrent Drug Use and Performance on the Stroop

This study enrolled treatment-seeking outpatients who were actively using cocaine and other drugs. In order to consider the possible effect(s) of drug use at the time of testing, urine toxicology tests were obtained on the day of testing. There were no differences between the completers and non-completers in the incidence of positive urine results for cocaine or poly-substance use (poly-substance = cocaine and at least one of the following: THC, amphetamines, benzodiazepines, and opiates) on the day of testing. The majority of subjects tested positive for cocaine use (completers: 74% and non-completers: 67% ($\chi^2 = 0.53$, $p = 0.57$)). THC was the next most common drug present (completers: 24% and non-completers: 28%, Fisher's exact $p = 0.76$), followed by polysubstance use (completers: 24%, non-completers: 22%, Fisher's exact $p = 1.00$). Benzodiazepine, amphetamine, and opiate use were minimal.

Effect of Cocaine Positive Urines on Stroop Results

Performance on the Stroop subtests was next considered in 2×2 between-subjects factorial ANOVAs with group (completer and non-completer) and cocaine use (negative and positive), as measured by urine tests on the day of testing, acting as independent variables. The ANOVAs

replicated previously found differences between completers and non-completers; specifically, main effects of trial completion upon color naming ($F(1,67) = 7.46$, $p = 0.008$), interference ($F(1,67) = 9.15$, $p = 0.004$), and derived interference ($F(1,67) = 6.07$, $p = 0.016$) were found, but no main effect of trial completion was found for word reading ($F(1,67) = 2.32$, $p = 0.13$). Conversely, no main effects of cocaine use upon any of the performance scores were found, though there was an interaction between trial completion and cocaine use for color naming ($F(1,67) = 4.74$, $p = 0.033$), with positive use impairing color-naming scores in the non-completers, but not in the completers.

Group Differences in Cocaine Use as Measured by Urine BE Levels

Urine data were available for 65 subjects, 50 of whom were completers and 15 of whom were non-completers. Baseline urine data were available for 46 of the former group. The relationship between average BE values (sum of log-transformed quantitative BE values/number of urine samples) and group was explored. Completers ($M = 8.36$, $SD = 1.49$) and non-completers ($M = 8.00$, $SD = 1.53$) did not exhibit differential average baseline urine BE levels ($F(1,59) = 0.67$, $p = 0.42$).

Urine BE Levels and Neuropsychological Test Performance

The relationships between urine BE levels and Stroop subtest performance scores were next considered. Average baseline urine BE levels did not significantly correlate with baseline performance scores ($N = 61$) on any of the subtests: color naming ($r = -0.20$, $p = 0.12$), word reading ($r = -0.11$, $p = 0.40$), and interference ($r = -0.08$, $p = 0.54$). Average urine BE levels over the entire trial correlated with baseline performance ($N = 65$) on the color naming ($r = -0.28$, $p = 0.022$), but not the word reading

($r = -0.11$, $p = 0.41$) or interference ($r = -0.12$, $p = 0.36$) subtests. When a Bonferroni correction for multiple analyses was performed, the α -level decreased to 0.008, rendering all of the correlations nonsignificant.

Another series of ANCOVAs on Stroop subtests included baseline poly-substance Triage[®] results as a covariate and trial completion (completers ($N = 45$) and non-completers ($N = 18$)) as the independent variable. Main effects of trial completion remained significant for color naming ($F(1,60) = 9.22$, $p = 0.004$, $\eta_p^2 = 0.13$), word reading ($F(1,60) = 5.52$, $p = 0.022$, $\eta_p^2 = 0.08$), interference ($F(1,60) = 8.52$, $p = 0.005$, $\eta_p^2 = 0.12$), and derived interference ($F(1,60) = 4.07$, $p = 0.048$, $\eta_p^2 = 0.06$). Baseline poly-substance use did not exhibit an independent effect in any of the analyses.

DISCUSSION

There was a significant difference between the completers and non-completers on the performance scores of color naming and interference after a Bonferroni correction for multiple analyses. The decreased performance on the interference subtest by the non-completers is consistent with the primary hypothesis that poor performance on the Stroop interference subtest would predict treatment dropout.

Three predictive models based on logistic regression were considered in the study: the Stroop model using only Stroop task subscale scores (ie color naming, word reading, and interference); the HDRS model using only the HDRS scores; and the Stroop and HDRS model using both the Stroop task subscale scores and HDRS scores. These models were evaluated by considering sensitivity, specificity, positive predictive values, and negative predictive values. The HDRS model was dominated in all categories by the Stroop model and the Stroop and HDRS model. Therefore the focus of the discussion will be on the models that employ the Stroop task subscales. The Stroop and HDRS model has a superior specificity and positive predictive value compared with the Stroop model. However, the Stroop model had superior sensitivity and negative predictive value. The choice of which model to use would depend on the relative importance of identifying completers *vs* non-completers. If the primary concern is the correct identification of non-completers such that additional resources could be employed to improve retention in treatment, then the Stroop model would be the preferred model. It should be noted that subjects in this study were at most mildly depressed based on HDRS scores and the importance of the HDRS in more severely depressed subjects cannot be commented on. The improvement in prediction ability of the model after the addition of the HDRS scores suggests that affective state contributes to treatment compliance. This is not surprising as decreased activity in the cingulate cortex and other prefrontal regions has been reported in both depressed individuals and cocaine-dependent individuals with impaired performance on the Stroop (Mayberg, 1997; Bolla *et al*, 2004). Most reports of neuropsychological testing in cocaine-dependent subjects have been completed when subjects are in varying degrees of abstinence (Manschreck *et al*, 1990; O'Malley *et al*, 1992; Mittenberg and Motta,

1993; Beatty *et al*, 1995; Bolla *et al*, 1998, 1999, 2000). The current study differed from previous studies in that subjects were outpatients and still actively using cocaine and other drugs. Notably, there were no differences between completers and non-completers for the presence of cocaine or other tested substances of abuses in urine samples obtained on the day of testing. The presence of cocaine alone or polysubstance use on the day of testing was not associated with performance scores on the three Stroop subtests, nor was there a trial completion \times cocaine use interaction.

In addition to urine toxicology results on the day of testing, a quantitative assessment of cocaine use during the baseline and treatment period was made using log-transformed quantitative urine BE levels. There was no significant difference in baseline quantitative assessments between the groups and no correlations were found between baseline quantitative BE values and performance on the Stroop subtests. Combined baseline and treatment quantitative cocaine urine BE levels correlated with color naming but not word reading or interference, though the former finding was not significant after correcting for multiple analyses. Prior studies have reported a relation between the amount of cocaine use as determined by self-report and performance on neuropsychological tests in abstinent cocaine-dependent subjects (Bolla *et al*, 1999). The differences in the use of self-report *vs* urine analysis as a measure of cocaine use and abstinent *vs* actively using cocaine-dependent subjects may explain the differences in the results.

One notable strength of this study is the inclusion of carefully screened, well-matched groups. A strength and weakness of the study is the ongoing use of cocaine and other substances of abuse. While the degree of substance use was not controlled for, there was no difference between groups for the percentage of positive urines for cocaine metabolites or other substances of abuse on the day of testing, nor was there a difference between quantitative urine BE values. The presence of ongoing cocaine use increases the generalizability of these findings to actively using cocaine-dependent subjects.

There is mounting evidence that the prefrontal cortex (PFC) and associated circuits are affected by cocaine dependence (Goldstein and Volkow, 2002). Anatomic studies of cocaine-dependent individuals have identified the following changes in the PFC: reduced gray matter (Franklin *et al*, 2002; Matochik *et al*, 2003), decreased white matter integrity (Lim *et al*, 2002), and increased white matter hyperintensities (Lyoo *et al*, 2004). Physiologic studies have shown decreased metabolism in the orbito-frontal cortex (Volkow *et al*, 1988) and increased cerebrovascular resistance in the arteries that supply the PFC (Herning *et al*, 1999). Some reports of neuropsychological testing in cocaine using subjects have identified decreased performance on tests that require the support of prefrontal structures (Ardila *et al*, 1991; Berry *et al*, 1993; Beatty *et al*, 1995; van Gorp *et al*, 1999; Di Sclafani *et al*, 2002). A relationship between the amount of cocaine consumed and neuropsychological deficits in attention, planning, mental flexibility, executive function, and psychomotor function have been reported (Bolla *et al*, 1998, 1999, 2000). In a meta-analysis of 15 neuropsychological studies comparing cocaine-dependent subjects to normal controls, the majority

of studies indicated some deficits in attention, learning and memory, response speed, and some tasks of executive functions (Jovanovski *et al*, 2005). In this meta-analysis, cocaine-using subjects demonstrated decreased performance on the Stroop, suggesting impairment on this task is a common finding in this population.

A prepotent response is a habitual response that may not be appropriate for the current circumstance. An example would be driving on the right side of the road. This is an appropriate and prepotent response for drivers in the United States. However, when a United States driver goes to the United Kingdom, it is no longer appropriate to drive on the right side of the road, although it is still the prepotent response. Cognitive control is needed to consistently select driving on the left side of the road. However after an extended period of driving in the United Kingdom, the prepotent response through repetition can be changed from driving on the right side of the road to driving on the left side of the road. Using the same analogy for the behavior of cocaine-dependent individuals, the prepotent response in cocaine-dependent individuals is treatment non-compliance and cocaine use; however, the goal is to change the prepotent response to treatment compliance and abstinence.

Evidence that drug-related stimuli decrease the brain's ability to inhibit a prepotent response is provided by studies utilizing a modification of the original Stroop task, the emotional Stroop task. In this modification, the color words are replaced with words that are germane to the respective substance of abuse (eg beer for alcoholics and crack for cocaine-dependent individuals) (Cox *et al*, 1999; Hester *et al*, 2006). Longer interference scores for emotion-laden words are interpreted as a preoccupation with the drug-related stimuli. Increased interference time for drug-related words has been shown in subjects with dependence on cocaine (Copersino *et al*, 2004; Carpenter *et al*, 2006; Hester *et al*, 2006), alcohol (Bauer and Cox, 1998; Cox *et al*, 2002; Lusher *et al*, 2004), heroin (Franken *et al*, 2000), and nicotine (Gross *et al*, 1993; Wertz and Sayette, 2001; Waters *et al*, 2003). It has been proposed that this preoccupation with drug-related stimuli is a form of attentional bias thought to underlie relapse (Franken, 2003; Copersino *et al*, 2004).

A number of functional imaging studies using the Stroop in normal subjects have shown increased activation of the anterior cingulate cortex (ACC) (Pardo *et al*, 1990; Carter *et al*, 1995; Peterson *et al*, 1999; Gruber *et al*, 2002). An fMRI study of cocaine abusers, using a modified version of the Goldman Stroop task, demonstrated less activation of the left ACC and right lateral PFC and increased activation of the right ACC compared to controls (Bolla *et al*, 2004). Subjects with the highest cocaine use before the study showed the lowest activation of prefrontal structures suggesting that cocaine use compromises the activation of the prefrontal regions involved in executive function (Bolla *et al*, 2004). Using a GO-NO-GO paradigm that also requires the inhibition of a prepotent response, cocaine-using subjects exhibited greater errors of omission and commission and decreased activation of the ACC and right PFC compared to controls (Kaufman *et al*, 2003). Tasks of cognitive control involve at least two areas of the PFC, the dorsolateral prefrontal cortex (DLPFC), and the ACC

(MacDonald *et al*, 2000). The DLPFC is involved in representing and maintaining the attentional demands of the task in working memory, whereas the ACC monitors the competition between processes that conflict during task performance, such as when a task elicits a prepotent but inappropriate response (Carter *et al*, 1998; Kiehl *et al*, 2000; Barch *et al*, 2001).

Two cognitive functions that are relevant to this discussion are selective attention and cognitive control. Selective attention can be voluntary (active, directed, top-down, controlled) or involuntary (reactive, passive, bottom-up, automatic), with voluntary controlled attention being inversely proportional to automatic attention (Franken, 2003). Selective attention supports the behavior of processing relevant stimuli, while cognitive control, another top-down function, allows an individual to select the appropriate response, even when it is not the prepotent response (Carter *et al*, 1998; Kiehl *et al*, 2000; Barch *et al*, 2001). Cognitive control, as measured by the Stroop, is hypothesized to be a parallel-distributed system, which also has inherently limited capacity (Cohen *et al*, 1990). However, repeated selection of the weaker response can strengthen the pathway to that response, effectively shifting a weaker response to a prepotent response (Miller and Cohen, 2001).

In cocaine-dependent subjects, decreased performance on the Stroop and other tasks of cognitive control may be due to two related and additive factors. As cited above, there is substantial evidence that in cocaine-dependent individuals, prefrontal structures and functions dependent on prefrontal regions are different compared to controls. In addition to these anatomically localized dysfunctions, cocaine-dependent individuals respond to environmental stimuli in the form of drug-salient stimuli with attentional bias, a type of involuntary attention and ruminative craving, a form of working memory (Bonson *et al*, 2002). Increases in working memory demands are related to decreased performance on tests of cognitive control (Hester and Garavan, 2004). Continuing with the position that selective attention and cognitive capacity are both limited capacity systems (Miller and Cohen, 2001; Franken, 2003), drug-salient stimuli would decrease the capacity of these systems to perform in a top-down manner. It is worth noting that top-down/voluntary modes of performance in these limited capacity systems require the support of the DLPFC and ACC, the same regions that are activated by bottom-up/involuntary modes of performance during cocaine-related cue-induced craving in cocaine-dependent subjects as shown by fMRI and positron emission tomography studies (Grant *et al*, 1996; Maas *et al*, 1998; Childress *et al*, 1999).

In cocaine-dependent subjects, Stroop studies using either cocaine-related stimuli or incongruent-color word stimuli have both shown impairment (Hester *et al*, 2006). This suggests that the incongruent-color word stimuli version of the Stroop can be used to detect impaired performance in cocaine-dependent individuals for the purposes of identifying individuals at risk for treatment dropout. While both paradigms provide valuable information, the color word version of the Stroop task is widely available and can easily be incorporated into a treatment protocol, thus allowing individuals with decreased performance on such tasks to be identified (MacLeod, 1991).

As stated above, by repeatedly choosing a response, that response can be strengthened to become a prepotent response (Miller and Cohen, 2001). The Stroop task is a measure of an individual's ability to inhibit a prepotent response. It would be expected that cocaine-dependent subjects with poor performance on the Stroop with the associated impairment in response inhibition would be at increased risk for dropout early in treatment when the prepotent responses of cocaine use and treatment non-compliance have not yet been adequately addressed. Identification of and subsequent tailoring of interventions to address neurocognitive deficits and comorbid mood disorders, when applied at the early stages of treatment, may enhance compliance and thus retention among vulnerable individuals. With improved treatment retention comes further opportunities for implementing interventions targeted at shifting the prepotent response from drug use and treatment noncompliance to that of abstinence and treatment compliance.

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