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Baseline neurocognitive profiles differentiate abstainers and non-abstainers in a cocaine clinical trial

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Abstract

Previous studies have shown that cocaine users have higher levels of impulsivity and impaired decision making; however few have examined these factors as predictors of treatment success. We obtained baseline neurocognitive measures from 75 cocaine-dependent individuals participating in a 12-week clinical trial targeting impulsivity with behavioral therapies and pharmacotherapy. Subjects treated with citalopram (versus placebo) had higher cocaine abstinence rates compared to placebo-treated subjects (Moeller et al., 2007). The aim of this secondary analysis study was to determine whether profiles of performance on neurocognitive measures administered at baseline discriminated among patients who achieved abstinence and those who did not. Subjects completed the Immediate and Delayed Memory Task (IMT/DMT), Barratt Impulsiveness Scale (BIS-11), and Iowa Gambling Task (IGT). Profile analysis results showed different patterns of performance on these baseline measures as a function of outcome. Compared with non-abstinent participants, abstinent subjects had higher scores on the BIS-11 Non-Planning subscale and better performance on the IGT. Profile differences for the two outcome groups did not vary as a function of treatment condition. Results suggest that cocaine dependent patients entering treatment with higher impulsivity and less impaired decision-making abilities may respond favorably to targeted behavioral interventions. Neurocognitive profiles may be useful in understanding population heterogeneity and predicting differential outcomes in subgroups of cocaine abusers.

Keywords

impulsivity; decision making; cocaine; cognitive behavioral therapy; contingency management; citalopram; profile analysis

1. Introduction

A substantial body of neuroimaging studies show important differences in the brains of cocaine users relative to normal controls, particularly regions in the prefrontal and orbitofrontal cortex e.g., [1, 2-5]. These areas govern several important higher cortical functions, including response

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inhibition and advantageous decision-making[6]. Consistent with these brain imaging findings, cocaine users have demonstrated higher levels of impulsivity[7-11] and poorer decision making performance[4, 12, 13] compared to non-cocaine using controls. These neurocognitive deficits negatively predict treatment participation and completion[10, 14], prompting the need to design interventions that target impulsivity in cocaine dependent individuals.

The link between serotonin function and impulsivity (reviewed in 15) has provided the rationale for using selective serotonin reuptake inhibitors (SSRI) agents for treatment of cocaine dependence. In a previous report based on data collected from the present trial, we found that the SSRI citalopram was effective in reducing cocaine positive urines 16. In addition to the medication intervention, all subjects in the trial received behavioral treatment consisting of contingency management (CM) and cognitive behavioral therapy (CBT). This evidence-based therapy platform was chosen specifically to address neuropsychological processes implicated in impulsiveness and addiction. By providing immediate delivery of monetary rewards contingent on abstinence, CM was considered appropriate for highly impulsive cocaine users who tend to prioritize immediate over delayed rewards17. CBT, often used in conjunction with CM, targets decision-making by helping patients re-learn how to anticipate and adaptively cope with complex, high-risk situations. The extent to which deficits in these processes are associated with response to behavioral treatment in cocaine users is not completely understood.

This study used baseline measures of impulsivity, decision making, and behavioral inhibition in cocaine dependent patients and evaluated the extent to which deficits in functioning predict abstinence outcomes. We expected that addressing deficits in impulsivity and decision making with the CM and CBT platform would moderate the predictive value of these mechanisms. Unlike other studies, we were interested in identifying pretreatment neurocognitive profiles associated with treatment outcome. Focusing on profiles rather than single measures of impulsivity is consistent with the writings of Bechara[18] and others[15, 19] who conceptualize impulsiveness as a multifaceted construct, requiring a battery of tasks to optimally characterize the role of contributing components. Thus, we expected that a baseline profile indicating higher impulsivity would be associated with better outcome in the context of the targeted behavioral treatment. The extent to which this association varied as a function of medication treatment was examined as well.

Methods

Subjects

We recruited 157 treatment-seeking cocaine-dependent adults from the community (for complete methodological details please see 16). Following orientation and informed consent procedures, subjects were screened for concomitant Axis I disorders using the Structured Clinical Interview for DSM-IV (SCID)20. Eligible subjects met criteria for cocaine dependence, but no other Axis I disorders. Seventy-five subjects met the inclusion criteria, were randomized, and entered the 12-week treatment phase. The most common exclusionary reasons were having a serious non-psychiatric medical condition, having a concomitant Axis I disorder, and failing to meet criteria for cocaine dependence. The final sample of subjects was African American (73%) men (86%), with a mean age of 39 ± 7.5 years. On average subjects in the study had a high school diploma or equivalent, with a range of education level from grade 6 to completion of graduate or professional school. The mean lifetime history of cocaine use was 11.58 ± 7.3 years.

This study was approved by the Committee for the Protection of Human Subjects of the University of Texas Health Science Center at Houston (Clinicaltrials.gov Identifier: NCT00297505).

Procedures

Following randomization and prior to treatment onset, measures of impulsivity and decision-making were administered. Subjects then began the 12-week trial of pharmacotherapy (placebo or citalopram, 20 mg/day). All subjects received the behavioral treatment platform consisting of 60-minute weekly individual cognitive-behavioral therapy (CBT) sessions and abstinence-based contingency management (CM) therapy.

Behavioral therapy

The CM procedure followed the reinforcement schedule recommended by Budney and Higgins[21] in which reward vouchers were delivered contingent on cocaine-negative urine samples, starting at a monetary value of $2.50 and escalating by $1.25 for each consecutive negative urine. A $10 bonus voucher was awarded for providing three consecutive cocaine-negative urine samples. Missed or refused samples were considered positive and reset the voucher value to $2.50. Five consecutive negative urines after submission of a positive urine sample could return the voucher value to its previous level. Vouchers earned could be exchanged at any time for gift certificates (e.g., local restaurants, movie theatre).

CBT sessions focused on training and mastery of behavioral and cognitive skills for coping with situations associated with drug use. Using a directive style, therapists assist clients in recognizing high risk situations and in developing new responses (thoughts and actions) to resist drug use. A step-by-step problem-solving approach22 is taught and applied throughout the course of treatment. Therapy strategies include in-session use of role-playing, modeling, and didactic presentations and between-session use of self-monitoring and practice assignments. Master's-level therapists underwent initial training to establish competence and adherence prior to delivery of the manual driven CBT (evaluated previously in 23, 24). For ongoing supervision, therapists met weekly with a senior therapist who reviewed manual adherence and clinical case materials. Adherence ratings conducted on a randomly selected sample of the audio-taped sessions showed no evidence of significant drift from the manual.

Measures

Impulsivity—The Immediate and Delayed Memory Task (IMT/DMT)25, 26 is a computerized continuous performance task used to assess attentional and inhibitory-control components of impulsivity. A series of 5-digit numbers (e.g., 73021) are displayed on the monitor for 0.5 s and separated by a 0.5 s blackout period. There are several distinct types of stimuli presented and types of responses that can be made. Subjects are instructed to respond when a 5-digit number (the target stimulus) appears that is identical to the preceding stimulus. The probability of a target stimulus is set at 33%. A response made while a target stimulus appears on the monitor, or made before the next stimulus appears (1.0 s total), is recorded as a correct detection (or “hit”). A failure to respond to a target stimulus is recorded as an omission error (or “miss”). In addition to target stimuli, there is a 33% probability that a catch stimulus will appear. A catch stimulus is a number that differs from the preceding number by one of the five digits (its position and value is determined randomly). Responses (errors) made to catch stimuli are considered commission errors (or “false alarms”). Novel stimuli (numbers) that are not either target or catch trials (34% of the stimuli) are called filler stimuli and responses made to these stimuli are called random errors. Correct detections are often used as a measure of attentional capacity, and commission errors are often used as a laboratory measure of behavioral inhibition.

The Barratt Impulsiveness Scale - 11 (BIS-11)[27] is a 30-item self-report measure of impulsivity that indexes a variety of impulsive acts and long-term behavioral patterns. The BIS provides a total score as well as three subscale scores labeled non-planning, attentional, and motor impulsivity based on a principal component analysis27.

Decision Making—A computerized version of the original Iowa Gambling Task (IGT)28 was used, in which subjects are asked to choose between four decks of cards that result in theoretical monetary rewards at different rates. Each deck (labeled A, B, C, and D) contains 60 cards. Subjects must make 100 choices over the testing session. Healthy controls are able to determine that two decks of cards lead to small immediate monetary rewards but over the long-term are more advantageous due to large losses in the other two decks of cards. This task has been able to differentiate between patients with frontal cortical lesions and controls29, 30, and drug users and controls31. The net score for the Iowa Gambling Task is calculated as the total number of cards selected from the advantageous minus the disadvantageous decks ((C +D)-(A+B)) across five blocks of 20 cards each.

Cocaine use—Urine samples were collected at three clinic visits during the one-week pretreatment baseline period, and at each twice-weekly clinic visit during the 12-week treatment period; hence a total of twenty-seven urine samples were collected over time. Urine specimens were also tested qualitatively for the presence of benzoylecgonine (BE) using the Syva EMIT System and Ansys Diagnostics Toxi-Lab thin layer chromatographic system. Specimens with concentrations exceeding 300 ng/mL BE were coded positive for the cocaine metabolite.

Statistical Analysis

All analyses were conducted with the Statistical Analysis System Version 9.1.3 [32]. Values of $p < .05$ were considered statistically significant, based on two-tailed tests. Two treatment outcome groups were operationally defined as abstainers (≥ 4 consecutive cocaine-negative urines) or non-abstainers (< 4 consecutive cocaine-negative urines). Two consecutive weeks of abstinence (i.e., 4 consecutive cocaine-negative urines) is regarded in the treatment literature as clinically meaningful and commonly used as a primary efficacy outcome measure e.g., [33, 34, 35]. Pharmacologically, two weeks is considered to be of sufficient duration to detect neurobiologic and physiological changes resulting from cocaine discontinuation [36, 37]. Cox proportional hazards survival analysis was used to examine differences in retention (i.e., weeks remaining in study) as a function of outcome status (abstinent, non-abstinent) and baseline neurocognitive measures, with medication condition (0, placebo; 1, citalopram) included as a covariate.

Profile analysis (PA), essentially a repeated-measures MANOVA38, 39, tested groups defined by outcome for differences on the multivariate profile of six dependent variables: the two IMT/DMT scores; the three subscales of the BIS-11; and the IGT net score. As suggested39, PA was carried out on standardized scores, which was accomplished by z-scoring each of the indices to have a mean of 0 and a standard deviation of 1. Specific tests for parallelism, level, and flatness were used to characterize different patterns of responding between groups. In order to ascertain the degree to which differential profiles for treatment outcome groups may, themselves, have differed as a function of treatment condition, the initial model included outcome group, treatment condition and their interaction. Follow-up tests to parse any differences in profiles across groups utilized standard univariate analyses, implementing the False Discovery Rate (FDR) to control for multiple comparisons40.

Results

Baseline Comparisons

Fifteen individuals achieved abstinence criteria while 60 did not. The two outcome groups did not differ on baseline demographic or drug history variables (see Table 1). In a Cox proportional hazard regression model, controlling for the effects of medication assignment, retention in study differed by outcome group $\chi 2\ (1) = 5.46$, $p = 0.01$, with abstainers more likely to remain

in treatment than non-abstainers. None of the indices of impulsivity and decision-making were predictive of treatment retention, DMT false alarms, $\chi 2$ (1) = 0.002, p = 0.95, IMT false alarms, $\chi 2$ (1) = 0.67, p = 0.41, BIS-11 score, $\chi 2$ (1) = 1.74, p = 0.18, and IGT choices, $\chi 2$ (1) = 0.22, p = 0.65.

Profile Analysis

Initial evaluation of the profile analysis model revealed that there was not a significant interaction between medication condition and outcome: for parallelism, Wilks' Lambda = 0.89, F (5, 59) = 1.41, p=0 .23; for flatness, Wilks' Lambda = 0.94, F (5, 59) = 0.78, p=0.57; and for levels, F (1, 63) ≤ 0.01, p=0.99. Subsequently the interaction term was removed from the model.

The test of differential shapes (parallelism), as a function of outcome group, failed to find an effect (Wilks' Lambda = 0.86, F (5, 61) = 1.91, p≤ .11). Collapsing across outcome groups, the test of flatness failed to demonstrate an effect, i.e., reject the hypothesis that the measures exhibited a flat profile (Wilks' Lambda = 0.95, F (5, 61) = 0.69, p≤ .63). A levels effect emerged, F (1, 65) = 6.80, p≤ .0109, indicating that reliable differences were found between outcome groups when scores were averaged across multiple measures. These differences were in the direction of the abstinent group scoring higher on average across all baseline measures. Follow-up tests comparing group differences on the means demonstrated effects for the IGT (p < .009; FDR <.042) and the BIS-Non-Planning subscale (p < .010; FDR <.042), as shown in Figure 1.

Discussion

In this sample of participants receiving behavioral therapy in the context of a randomized clinical trial, we found that treatment outcome status, i.e., abstinent or nonabstinent from cocaine for 2 or more weeks, was associated with different neurocognitive profiles measured at baseline. Abstinent subjects were more impulsive, as measured by the BIS non-planning scale, while, at the same time, more likely to use advantageous decision-making strategies, as measured by the IGT. The results for the BIS differ from a previous study by our group which did not use CM or CBT and found that higher impulsivity was associated with a poorer treatment response[14].

Based on the therapy design for this study, we expected that higher impulsivity, which is related to choice of immediate over delayed rewards[15], would positively predict responding to the immediate monetary-based rewards offered as part of contingency management. Likewise, we hypothesized that decision-making on the IGT, which involves responding flexibly to changing contingencies, would be associated with favorable response to CM. Finally, we proposed that having more intact cognitive processes would facilitate responding to CBT skills training. Our findings support this notion that monetary incentives combined with skills training may be a strong treatment intervention for a subgroup of impulsive cocaine patients. Without a therapy control condition, we cannot determine the relative efficacy of CM with CBT over other behavioral or nonbehavioral treatment interventions. Nevertheless, our findings contribute to a growing literature of studies reporting a significant relationship between baseline neurocognitive function and clinical outcome in drug using patients following treatment[41, 42]. Further investigation of the specific efficacy of behavioral treatment for targeting impulsivity in cocaine dependent subjects is needed.

The role of impulsivity in the initiation and maintenance of stimulant abuse has drawn increasing attention. Notions of impulsivity have emphasized lack of inhibition, rapid responding, lack of persistence, inattentiveness, and failure to delay reward gratification [15, 43]. In this study we observed that self-reported indexes of nonplanning impulsivity were associated with cocaine abstinence, whereas indexes of attentional, motor, and inhibitory-

control components of impulsivity, as assessed by the IMT/DMT and the BIS-11, failed to predict treatment retention or demonstrate a difference as a function of cocaine abstinence. These measures have previously shown differences between normal controls and cocaine users [44]. The lack of influence on these processes on treatment response suggests that not all components of impulsivity are equally predictive of treatment response.

The current report has several limitations. First, measures of impulsivity and decision making were not fully representative of these domains. A measure of delay of reward gratification, such as a delay discounting procedure, would have strengthened our findings. Moreover, other indexes of executive function, such as the Wisconsin Card Sort task, would have provided more evidence of the role of decision making in treatment response. As mentioned earlier, no treatment condition was included without CM and CBT, making conclusions about the role of behavioral interventions tentative. That abstainers were more likely to remain in study than non-abstainers means that level of exposure to, and participation in, therapy varied, which may have also confounded interpretation of the findings. Statistically, the lack of interaction between medication condition and behavioral measures could have been a function of power; the idea that differential profiles for outcome groups are themselves moderated by treatment condition remains plausible. Finally, the current sample was restricted to a narrow range of severe cocaine users, and inclusion of the full continuum of cocaine abusers might have altered the current results.

In summary, this study found that neurocognitive profiles, obtained from cocaine dependent subjects at baseline, differed as a function of treatment outcome. Subjects who achieved at least 2 weeks of abstinence had higher non-planning impulsivity scores and better decision-making performance at baseline than subjects who failed to achieve abstinence. These differences were observed within the context of a behavioral therapy platform designed to target impulsivity. While these findings cannot establish a causal relation between cognitive function at baseline and response to specific therapeutic interventions, they permit speculation regarding appropriate treatment-matching strategies and underscore the need for future confirmatory research.

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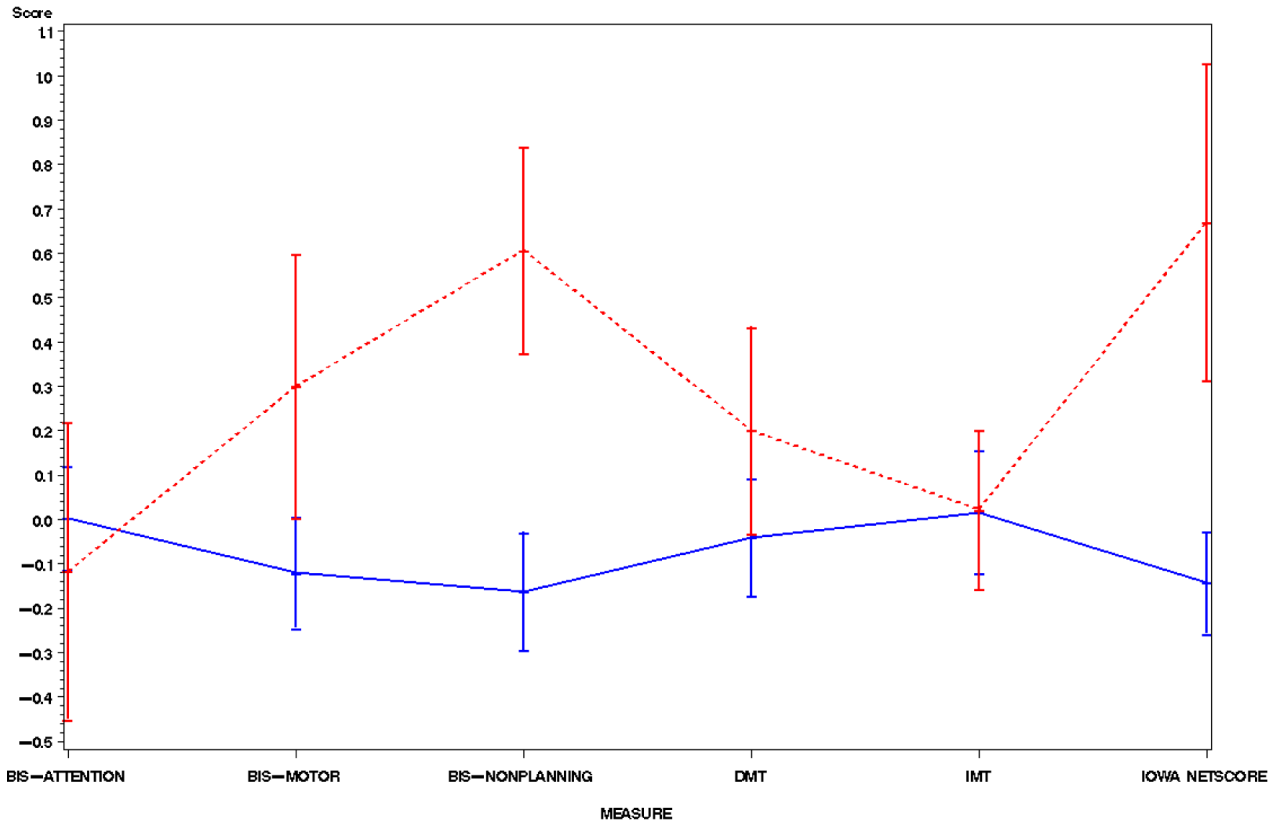

Figure 1.

Profile analysis of baseline scores on measures of impulsivity and decision-making as a function of outcome group (non-abstinent, solid line; abstinent, dashed line). The IMT/DMT was summarized using false alarms. The BIS-11 was summarized with its three factors scores: attentional, motor, nonplanning. The IGT was represented by the net score. All scales were standardized as z-scores ($M = 1$, $SD = 0$) with error bars representing ±SEM.

Table 1

Sample characteristics

	Outcome group	
	Abstinent (n=15)	**Non-abstinent (n=60)**
Age	39.6 (7.7)	38.7 (7.3)
% Female (n)	20.0 (3)	11.6 (7)
% White (n)	20.0 (3)	23.3 (14)
Years using cocaine, M (SD)	15.4 (8.5)	10.5 (6.5)
% non-abstinent during baseline (n)	73.0 (11)	93.0 (56)
Study visits attended, M (SD)	17.2 (8.2)	7.3 (7.4)
% citalopram condition (n)	53.3 (8)	45.0 (27)
% placebo condition (n)	46.6 (7)	55.0 (33)