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Increased intra-individual reaction time variability in cocaine-dependent subjects: role of cocaine-related cues

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Abstract

Neuroimaging data suggest that impaired performance on response inhibition and information processing tests in cocaine-dependent subjects is related to prefrontal and frontal cortical dysfunction and that dysfunction in these brain areas may underlie some aspects of cocaine addiction. In subjects with attention-deficit hyperactivity disorder and other psychiatric disorders, the Intra-Individual Reaction Time Variability (IIRTV) has been associated with frontal cortical dysfunction. In the present study, we evaluated IIRTV parameters in cocaine-dependent subjects vs. controls using a cocaine Stroop task. Fifty control and 123 cocaine-dependent subjects compiled from three studies completed a cocaine Stroop task. Standard deviation (SD) and coefficient of variation (CV) for reaction times (RT) were calculated for both trials with neutral and trials with cocaine-related words. The parameters μ , σ , and τ were calculated using an ex-Gaussian analysis employed to characterize variability in RTs. The ex-Gaussian analysis divides the RTs into normal (μ , σ) and exponential (τ) components. Using robust regression analysis, cocaine-dependent subjects showed greater SD, CV and τ on trials with cocaine-related words compared to controls ($p < 0.05$). However, in trials with neutral words, there was no evidence of group differences in any IIRTV parameters ($p > 0.05$). The Wilcoxon matched-pairs signed-rank test showed that for cocaine-dependent subjects, both SD and τ were larger in trials with cocaine-related words than in trials with neutral words ($p < 0.05$). The observation that only cocaine-related words increased IIRTV in cocaine-dependent subjects suggests that cocaine-related stimuli might disrupt information processing subserved by prefrontal and frontal cortical circuits.

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Contributors

Shijing Liu contributed to writing of the manuscript, analyzed all data, interpreted the data, and participated parts of data collection. F. Gerard Moeller, Scott D. Lane, Kathryn A. Cunningham and Joy C. Schmitz contributed to study design, data interpretation, and overall editing. Charles E. Green conducted statistical analysis and participated in data interpretation and overall editing. Shijing Liu wrote the first draft of the manuscript and all authors contributed to and have approved the final manuscript.

Conflict of Interest

There are no conflicts of interest in this manuscript.

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Keywords

Intra-individual reaction time variability; Ex-Gaussian analysis; Cocaine Stroop task; Cocaine dependence

1. Introduction

Poor performance on behavioral tasks related to prefrontal and frontal cortical function in cocaine-dependent subjects suggests that dysfunction in these regions may underlie some aspects of cocaine addiction, a hypothesis supported by recent neuroimaging studies (see review by Goldstein et al., 2002). Many of these behavioral tasks have used response-inhibition and information processing paradigms. In such paradigms, reaction time (RT) is a key index. Most studies have focused on averaged between-group differences in accuracy or RT. However, trial-by-trial fluctuations in RTs (intra-individual RT variability or IIRTV) also provide important information about performance beyond that provided by the overall means. Specifically, RTs on these tasks are not normally distributed, characterized by clusters of unusually long RTs that skew the distribution to the right. This rightward skew can be described by ex-Gaussian analysis, which focuses on the non-normal segment of the distribution (Buzy et al., 2009; Lacouture et al., 2008).

Increased IIRTV has been found in subjects with different psychiatric disorders. For example, children with attention deficit and hyperactive disorder (ADHD) show consistently increased IIRTV compared with healthy controls across different behavioral tasks and studies (Castellanos et al., 2005; Di Martino et al., 2008; Johnson et al., 2007; Klein et al., 2006; Leth-Steensen et al., 2000; Vaurio et al., 2009) although they exhibit mixed performance on behavioral tasks measuring inhibitory control (Lijffijt et al., 2005). In addition, across several studies using a variety of behavioral tasks, the IIRTV difference (rightward skew) has been reported in aging (vs. younger) populations of subjects (Anstey et al., 2005; Hulstsch et al., 2002; Myerson et al., 2007). The IIRTV parameters have been associated with biomarkers of age such as grip strength and visual acuity (Anstey et al., 2005).

The IIRTV can be calculated as the standard deviation (SD) or coefficient of variation (CV) of the RTs; CV is the SD divided by the mean RT. Because the RTs in behavioral task usually are not normally distributed but skewed to the right, an ex-Gaussian analysis has been used to characterize the IIRTV (Buzy et al., 2009; Lacouture et al., 2008). The ex-Gaussian analysis fits the RTs using two distributions: normal and exponential. It has three parameters: *mu*, *sigma*, and *tau*. *Mu* and *sigma* represent the mean and the SD of the normally distributed component, respectively. *Tau* describes both the mean and the SD of the exponential component, thereby providing a RT index of less frequent but usually long RTs. Larger values of *tau* indicate greater skew in the RT distribution (Buzy et al., 2009; Lacouture et al., 2008). In subjects with ADHD, *tau* has been a useful measure of RT performance (Buzy et al., 2009; Castellanos et al., 2005; Leth-Steensen et al., 2000). In the present study, we calculated SD, CV and *mu*, *sigma* and *tau* in the ex-Gaussian analysis using RTs from a modified Stroop task employing cocaine-related and neutral words.

Few studies have investigated IIRTV in drug dependence. Kollins et al. (2009) compared the differences in IIRTV from a continuous performance test between smokers with ADHD and without ADHD. This study showed that abstinence from nicotine increased the IIRTV in ADHD, but not in non-ADHD, subjects. However, this study did not include non-smokers as control subjects.

The cocaine Stroop task was designed to measure attentional bias to cocaine-related stimuli, recording RTs to indicate the colors of neutral or cocaine-related words. Attentional bias to cocaine-related words is the difference between the RT to indicate colors of cocaine-related vs. neutral words. Several studies have shown that cocaine-dependent subjects have greater attentional bias to cocaine-related words compared to control subjects (Hester et al., 2006; Liu et al., 2011). In the present study, we assessed the IIRTV of cocaine Stroop task performance in controls and cocaine-dependent subjects. Because (a) cocaine is a dopamine transporter blocker, (b) chronic cocaine use produces neural adaptations that result in a hypo-dopaminergic state (Mateo et al., 2005), and (c) cocaine-dependent individuals have deficiencies in attention and information processing similar to individuals with ADHD (see reviews Garavan et al., 2007; Jovanovski et al., 2005) we expected to find similar skewing in RT distributions reported in other clinical groups. Furthermore, due to the disruptions in performance produced by drug-related stimuli in tasks of attentional control (Hester et al., 2006; Liu et al., 2011; Waters et al., 2003), we expected the IIRTV to be greater in the presence of cocaine words vs. neutral words.

2. Materials and Methods

2.1. Subjects

The sample consisted of $n = 50$ control subjects and $n = 123$ active cocaine-dependent subjects recruited from three different studies using the same diagnostic, psychometric, and advertising procedures. Subjects were recruited via newspaper advertisements, screened for psychiatric disorders using the structured clinical interview for DSM-IV (SCID-I) (First et al., 1996), and completed a medical history and physical examination. All subjects were tested for urine cocaine (benzoylecgonine), tetrahydrocannabinol, opiates, amphetamine, methamphetamine and benzodiazepines using integrated E-Z split key cup II (Innovacon Company, San Diego, CA, USA) on each visit in the laboratory. Cocaine-dependent subjects met current DSM-IV criteria for cocaine dependence; had at least one cocaine positive urine during screening; did not meet DSM-IV current dependence criteria for abused drugs other than cocaine, marijuana, nicotine or alcohol; did not have current or past medical disorders affecting the central nervous system; and did not have axis I disorders other than substance abuse or dependence. Cocaine-dependent subjects included non-treatment-seekers and treatment seekers. The treatment-seekers were tested during the baseline period of a treatment study, prior to the start of medication or cognitive-behavioral therapy. Control subjects consisted of participants who did not have a positive drug screen and did not have any current or past DSM-IV axis I disorder (including substance dependence) or medical disorder affecting the central nervous system. All subjects were free of alcohol at the time of testing as determined by a breathalyzer (Intoximeters, Inc., St. Louis, MO, USA). Female subjects were excluded if they had a positive urine pregnancy test. All data were collected in the Center for Neurobehavioral Research in Addictions of University of Texas Health Science Center at Houston. Subjects were fully informed of the nature of the research and provided written consent for their involvement in accordance with the Declaration of Helsinki. The study was approved by the Committee for the Protection of Human Subjects of University of Texas Health Science Center at Houston.

2.2. Cocaine Stroop Task

This task was designed to measure attentional bias to cocaine-related stimuli (Hester et al., 2006; Liu et al., 2011). Each session included 60 practice trials and 240 test trials. The stimuli in the practice trials were colored repeated single letters matched in length to cocaine-related words (e.g., XXX, MMMMM). The stimuli in the test trials included 10 cocaine-related words "COCAINE," "CRACK," "ROCKS," "HIGH," "DEALER," "HIT," "SMOKE," "PUFF," "PIPE," "FREEBASE" and 10 length-matched neutral words

“CABINET,” “COUCH,” “SOFA,” “OVEN,” “FLOOR,” “WINDOW,” “RUG,” “ARMCHAIR,” “LAMP,” “ROOM.” In each trial, the word was presented against a black background in one of three colors: red, blue, or green. Subjects were required to press colored buttons (blue, red, or green) to indicate the color of the words as quickly and as accurately as possible while ignoring the meaning of the words. The stimulus stayed on the screen until the subject made a button press or until 3000 msec had elapsed. The intertrial interval was 500 msec. The test trials included either 2 or 4 blocks of trials with cocaine-related words, and 4 or 6 blocks of trials with neutral words (block number varied across the three studies). Each block included 30 trials, in which each word was randomly presented three times in three different colors. Block type (cocaine or neutral) was alternated in counterbalanced fashion or randomly distributed. Because the number of blocks varied across the three studies, only the first block of trials with cocaine-related words and the first block with neutral words were used in the data analyses. The trials with correct responses and RTs larger than 200 msec were used to calculate mean RTs. The difference in mean RTs between trials with cocaine-related words and those with neutral words was used as a measure of attentional bias to cocaine-related words. The following parameters for the IIRTV were also calculated using trials with correct responses and RTs larger than 200 msec: RT SD and CV for trials with neutral words (NeuSD, NeuCV), RT SD and CV for trials with cocaine-related words (CocSD, CocCV), μ , σ and τ for trials with neutral words (Neu μ , Neu σ , Neu τ) and μ , σ , τ for trials with cocaine-related words (Coc μ , Coc σ , Coc τ). Ex-Gaussian parameter estimates (μ , σ , τ) were calculated using the egfit MATLAB function written by Lacouture and Cousineau (2008). This function performs an iterative search process to fit the ex-Gaussian probability density function to a frequency distribution, reporting the three parameters (μ , σ , τ) of the probability distribution from which the observed RTs would most likely be sampled.

2.3. Statistical Analyses

For general linear models (GLM) the Shapiro-Wilk test was used to assess the normality of residuals. Differences in demographic variables between groups were compared using the Mann-Whitney test for continuous variables (age and educational level) because residuals of both variables were not normally distributed (Shapiro-Wilk test $p < .05$). The chi-square test was used to analyze categorical variables. Differences between controls and cocaine-dependent subjects were analyzed using robust regression with age, gender and educational level as covariates for all the IIRTV parameters (NeuSD, NeuCV, Neu μ , Neu σ or Neu τ , CocSD, CocCV, Coc μ , Coc σ and Coc τ), as none of which had normally distributed residuals. Multiple linear regression was employed to analyze the attentional bias data, which was normally distributed. The Wilcoxon matched-pairs signed-rank test was used to evaluate differences in IIRTV parameters between trials with cocaine words and trials with neutral words in both groups. Given the pilot nature of the current study all tests were conducted with $p \leq 0.05$, with no correction for multiplicity. All analyses were done in STATA 11.1.

3. Results

The two groups did not differ significantly in ethnicity ($\chi^2=2.33$, $p=0.31$; 36 African Americans, 7 Caucasians, and 7 others in control group vs. 90 African Americans, 24 Caucasians, and 9 others in cocaine-dependent group). The cocaine-dependent subjects were older (Mann-Whitney test, $z = 7.40$, $p < 0.001$) than controls (43.61 ± 7.91 vs. 31.62 ± 7.84 years old), differed in gender distribution compared with controls ($\chi^2 = 16.28$, $p < 0.001$; 99 male, 24 female in cocaine-dependent group vs. 25 male, 25 female in control) and had a lower educational level (Mann-Whitney test, $z = -3.50$, $p = 0.001$, 12.77 ± 1.64 vs. $13.96 \pm$

2.16 years). All subjects had normal or corrected-to-normal vision and none were color-blind.

After fitting GLM to the IIRTV parameters, the Shapiro-Wilk test showed residuals for all dependent variables were not normally distributed ($p < 0.05$). Therefore, robust regression was used to compare parameter differences between control and cocaine-dependent subjects. The results failed to find differences for NeuSD, NeuCV, NeuMu, NeuSigma or NeuTau as a function of control and cocaine-dependent status after controlling for age, gender and educational level. As shown in Tables 1, 2 and 3, CocSD ($p = 0.005$), CocCV ($p = 0.024$) and CocTau ($p = 0.019$) were different between control and cocaine-dependent subjects after controlling for age, gender and educational level. There was no evidence for group differences for CocMu and CocSigma. In summary, IIRTV parameters were different between control and cocaine-dependent subjects only on trials in which cocaine-words were presented.

The Wilcoxon matched-pairs signed-ranks test was used to compare the differences of NeuSD and CocSD, NeuCV and CocCV, and NeuTau and CocTau, separately for control subjects and cocaine-dependent subjects. These outcomes are presented graphically in Figure 1, which shows means and standard error corrected for age, sex and educational level. The CocSD was larger than NeuSD in cocaine-dependent subjects ($z = 4.649$, $p < 0.001$, Figure 1A) but not in control subjects ($z = -0.208$, $p = 0.836$, Figure 1B). The difference between CocCV and NeuCV was not significant ($z = 1.916$, $p = 0.0554$, Figure 1B) in cocaine-dependent subjects or in control subjects ($z = -0.710$, $p = 0.478$, Figure 1B). The CocTau was significantly larger than NeuTau in cocaine-dependent subjects ($z = 3.665$, $p < 0.001$, Figure 1C) but not in control subjects ($z = -0.111$, $p = 0.9116$, Figure 1C). Figure 2 depicts the covariate (age, sex, educational level)-adjusted RT distributions for each group and word type (cocaine, neutral), showing clearly the skew in RT distribution between the two groups in the presence of cocaine-related words.

Attentional bias was calculated as the difference score between mean RT to neutral and cocaine-related words. The Shapiro-Wilk test of GLM-based residuals did not reject the normal distribution of attentional bias ($p > 0.05$). Therefore, multiple linear regression analysis was used to compare difference in attentional bias between groups. Controlling for age, sex and educational level, attentional bias was higher in cocaine-dependent subjects than in control subjects, ($t = 2.93$, $p = 0.004$; 78.24 ± 9.20 vs. 17.22 ± 10.33 msec).

4. Discussion

The cocaine Stroop task is designed to assess attentional bias to cocaine-related stimuli (Hester et al., 2006; Liu et al, 2011; Vadhan et al., 2007). On tasks demanding attentional control, RT distributions are often skewed in clinical groups with deficits in attention and information processing (e.g., ADHD, substance dependence). Given that trial-by-trial fluctuations in RTs also provide important information about performance beyond that provided by the overall mean RT, we examined trial-to-trial RT variability by comparing the IIRTV from our cocaine-Stroop task in control and cocaine-dependent subjects. Our results showed that controlling for age, sex and educational level, cocaine-dependent subjects showed greater SD, CV and Tau on trials with cocaine-related words compared to controls ($p < 0.05$). However, in trials with neutral words, there was no evidence of group differences in any IIRTV parameters ($p > 0.05$). The Wilcoxon matched-pairs signed-rank test showed that for cocaine-dependent subjects, both SD and tau were larger in trials with cocaine-related words than in trials with neutral words ($p < 0.05$).

Cocaine-dependent subjects showed greater IIRTV (*CocSD*, *CocCV* and *CocTau*) relative to controls. Importantly, IIRTV differences were obtained only in the presence of cocaine-related stimuli. IIRTV parameters were not different between groups on trials involving neutral stimuli; and only in the cocaine-dependent group was there a difference in IIRTV parameters between trials with neutral and cocaine-related words. Group differences on trials with neutral words would indicate more global attention and information processing deficits seen in other clinical disorders such as ADHD; we did not see indication of such deficits in the cocaine-dependent group.

In the cocaine-dependent group, there was no correlation between the IIRTV parameters and age, sex, educational level. Therefore, we conclude that for cocaine-dependent subjects the presence of cocaine-related words disrupted attentional and/or information processing systems required on this task, evident in greater skew (higher *Tau* and CV values) on cocaine-word trials relative to neutral-word trials. This hypothesis is consistent with theories of cue-induced psychological craving (Field et al., 2008). It is posited that through associative conditioning, drug-related stimuli become associated with drug-reinforcement processes, and these conditioned stimuli come to alter cognitive control mechanisms, including attention. Proposed sequelae of this process include biased attention to drug cues, the initiation of perseverative thinking about drug use, and the eventual development of compulsive or habitual drug-seeking and drug-taking behaviors (Field et al., 2008).

In animal studies, cocaine-associated stimuli trigger cocaine-seeking behaviors (see review by See, 2005); and the present data support previous work in human subjects showing that cocaine-related stimuli are known to produce attentional bias and other disruptions in information processing (Hester et al., 2006; Hester & Garavan, 2009; Liu et al., 2011; Vadhan et al., 2007; Woicik et al., 2009). Increased *Tau* values (exponential component of the ex-Gaussian distribution) without changes in *Mu* or *Sigma* (Gaussian component of the distribution) indicate performance characterized by intermittent, unusually slow responses attributed to lapses of attention (Buzy et al., 2009; Leth-Steensen et al., 2000; Kollins et al., 2009). In the present data, this relationship among *Tau*, *Mu*, and *Sigma* suggests that the attentional bias difference between cocaine-dependent and control subjects may have been due to periodic lapses in attention. Given that differences were observed only on cocaine-word trials, we conclude that such lapses were induced by the cocaine-related stimuli, which produced disruptions in cognitive control processes.

Several recent studies indicate that increased IIRTV is related to dysfunction in prefrontal and frontal cortical systems. Stuss et al. (2003) reported that subjects with frontal-lobe brain lesions showed increased IIRTV (SD and CV) compared with control subjects and subjects with non-frontal brain lesions. Using fMRI, Bellgrove et al. (2004) showed that task-related brain activation in bilateral middle frontal, right inferior parietal, and thalamic regions was positively correlated with IIRTV in healthy subjects performing a Go/NoGo task. Frontal lobe white matter hyperintensities (WMH, a putative marker of damage to white matter) were associated with increased IIRTV (Bunce et al., 2007), and IIRTV (SD) was correlated with white matter volume in healthy control subjects performing a visual oddball task (Walhovd et al., 2007). At the level of cortical networks, RT variability (highlighted by attentional lapses) appears to be mediated by abnormalities in the ongoing balance of activation between the default-mode network and the attentional network; both networks are broadly distributed across frontal, prefrontal, medial-temporal, and parietal regions (Fan et al., 2002; Kelly et al., 2008).

Cocaine dependence is also associated with dysfunction in frontal and prefrontal cortices (Beveridge et al., 2008; Goldstein et al., 2002). When cocaine users were exposed to cocaine-related stimuli, significant activation was found in anterior cingulate and left

dorsolateral prefrontal cortex compared with healthy control subjects (Mass et al., 1998; Gavavan et al., 2000). Correspondingly, the anterior cingulate cortex has been well established as a critical region subserving conflict monitoring during tasks of attentional and inhibitory processing (Botvinick et al., 2004; van Veen et al., 2004).

Given the overlapping associations among increased IIRTV parameters, cocaine dependence, and prefrontal-frontal cortical systems, it is plausible that the IIRTV differences we observed were mediated in part by a cocaine-related compromise in the functional integrity of these cortical regions. Additionally, to the extent that the default-mode network mediates mind wandering and memory retrieval (Buckner et al., 2008), long RTs (lapses in attention) may be the result of cocaine cues (over)activating this network in a task-incongruent manner. Future work will be needed to confirm these hypotheses. One step in the process will be to systemically replicate the present IIRTV findings (in the presence of cocaine-related stimuli) during neuroimaging protocols designed to map trial-by-trial RTs onto BOLD activation patterns.

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Highlights

- We compare reaction time variability between controls and cocaine users.
- Cocaine users show bigger variability than controls only when cocaine cues occur.
- Cocaine cues increase variability in cocaine users but not in controls.
- This suggests that cocaine cues may disrupt information processing in cocaine users.

Figure 1.

The IIRTV parameter comparison. The values were expressed as mean $\pm$ S.E. adjusted for age, sex and educational level. ^: $p < 0.05$, ^^: $p < 0.01$, vs. trials with cocaine words in control group, robust regression; *: $p = 0.055$, **: $p < 0.01$, vs. trials with neutral words in cocaine group, Wilcoxon matched-pairs signed-rank test. A. Standard Deviation (SD) of RTs; B. Coefficient of Variability (CV) of RTs; C. Tau in ex-Gaussian analysis.

Figure 2.
Reaction time distribution (all subjects, adjusted for age, sex and educational level)

Table 1

Controlling for covariates, cocaine-dependent subjects showed significantly larger standard deviation (SD) of reaction times in trials with cocaine-related words than in trials with neutral words.

CocSD	Coef.	Std. Err.	t	p	[95% Conf. Interval]
NeuSD	0.759	0.061	12.44	0.000	0.638 0.879
Group	43.897	15.573	2.82	0.005	13.147 74.647
Age	-0.030	0.723	-0.04	0.967	-1.458 1.397
Sex	9.789	12.637	0.77	0.440	-15.164 34.742
Edu	1.128	3.049	0.037	0.712	-4.894 7.149
_cons	11.248	47.394	0.24	0.813	-82.334 104.830

Controlling for covariates, cocaine-dependent subjects showed significantly larger coefficient of variation (CV) of reaction times in trials with cocaine-related words than in trials with neutral words.

Table 2

CocCV	Coef.	Std. Err.	t	p	[95% Conf. Interval]	
NeuCV	0.503	0.067	7.48	0.000	0.370	0.636
Group	0.040	0.017	2.28	0.024	0.005	0.074
Age	−0.0004	0.0008	−0.49	0.622	−0.002	0.001
Sex	0.022	0.014	1.56	0.120	−0.006	0.050
Edu	0.002	0.003	0.51	0.607	−0.005	0.008
_cons	0.083	0.055	1.50	0.135	−0.026	0.191

Table 3

Controlling for covariates, cocaine-dependent subjects showed significantly larger *Tau* of reaction time ex-Gaussian analysis in trials with cocaine-related words than in trials with neutral words.

<i>CocTau</i>	Coef.	Std. Err.	t	p	[95% Conf. Interval]
<i>NeuTau</i>	0.549	0.074	7.39	0.000	0.402 0.695
Group	52.020	21.125	2.37	0.019	8.308 91.732
Age	0.794	0.985	0.81	0.421	-1.150 2.740
Sex	13.168	17.203	0.77	0.445	-20.800 47.135
Edu	3.587	4.176	0.86	0.392	-4.659 11.833
_cons	-38.212	64.475	-0.59	0.554	-165.520 89.096