INCREASED RESPONSE VARIABILITY AND ATTENTIONAL LAPSES AFTER CHRONIC COCAINE SELF-ADMINISTRATION

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In humans, cocaine use has long been associated with poor attentional control and decreased efficiency in goal-oriented behavior. Animal models of these stereotypic drug effects, however, have thus far failed to produce quantifiable data sets in part because of a lack of species differences and analysis techniques. Recent work (Hervey et al. 2006) has successfully quantified attentional lapses in disorders such as ADHD through the analysis of response time variations in simple tasks, but this analysis has yet to be applied to the drug abuse scenario. To determine the effects of chronic cocaine administration on response time variability, 14 rhesus macaque monkeys (8 cocaine administering and 6 performance-matched controls) were subjected to a 50 trial simple attention task. This task was performed W-F prior to cocaine self-administration sessions in the test group. Treatment groups were compared to both each other and to baseline task sessions recorded prior to beginning the administration paradigm. In addition to typical measures of variability, an ex-Gaussian response time analysis was performed to quantify the contribution of attentional lapses to overall variability. The cocaine-administering group had a significantly higher response time standard deviation than their pre-administration sessions ($p<0.05$). No difference was observed between pre- and post-administration sessions for the control group. When ex-Gaussian methods were applied to the response time datasets, no differences were observed between groups in the normal mean (mu), suggesting that the variability increase in the cocaine group was due to an increased skew in the right tail of the response time distribution. Indeed, the cocaine group showed a significant increase in the value of tau(exponential value representing the distribution tail magnitude) post-administration versus tau pre-administration ($p<0.05$). These data suggest that cocaine administration leads to increased behavioral variability in simple response time tasks, and that this variability increase is primarily due to the prevalence of abnormally long responses. Similar results have been demonstrated in clinical disorders such as ADHD, suggesting both the relevance of the primate model in studies of attentional processing and the possible similarity in affected brain regions or transmitter systems.

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1.0 INTRODUCTION

Cocaine use continues to be a significant societal and economic cost throughout the world today (Substance Abuse and Mental Health Services Administration, 2008). Paramount to examining the addictive nature of this drug and its potent reinforcing effects on behavior is determining the cognitive deficits that are associated with its use. While many different cognitive impairments have been observed in cocaine users, attentional deficits are among the most consistently found. It is also quite possible that the specific impairments in attentional control are responsible for performance decreases observed in other cognitive tasks (Jovanovski et al., 2005). These clinical studies, however, suffer because of confounding factors such as preexisting conditions, poly-drug use, and inconsistent dosing. Given that the effects of cocaine are dose-related (Bolla et al., 1999), we have chosen to examine attentional control in a primate model of cocaine self-administration where many of these clinical confounds can be avoided.

In recent years, the analysis of response times has emerged as a valuable tool in identifying the cognitive impairments associated with many clinical conditions. Contrary to many previous studies that have focused on the mean response time of a clinical population for analysis of dysfunction, measures of intra-individual response time variability have become valuable diagnostic tools (Hervey et al., 2006). Of particular interest are disorders that are typically characterized by inconsistent responding throughout the course of a particular task, such as Attention-Deficit/Hyperactivity Disorder, or ADHD (Leth-Steensen et al., 2000; Klein et al., 2006). As early as 1999, Douglas found increased response time variability in ADHD subjects and postulated that this variability must be related to the lack of attentional control that defines this disorder.

While standard measures of variability, such as response time standard deviation, have been used for characterizing clinical populations, more extensive methods of analysis have been developed. Response time standard deviation, by itself, can be limited as an indicator of the trial-by-trial changes in response time that underlie intra-individual variability because the overall shape of the response time distribution is ignored (Castellanos and Tannock, 2002). For this reason, studies have begun to examine response time data using the theoretical construct known

as the ex-Gaussian response time distribution to more finely examine intra-individual variability (eg. Leth-Steensen et al, 2000; Douglas, 1999).

The ex-Gaussian analysis of response time distributions makes the assumption that the histogram of a subject's response time dataset can be decomposed into two components (Burbeck and Luce, 1982). The breakdown into these components, referred to as mu (μ) and tau (τ) assumes that response time distributions consist of independent types of responses (and therefore two separate cognitive processes). The μ value provides the Gaussian or normal mean of the response time distribution, which is essentially the mean value when the distribution is assumed to be normal and the right-tail has been removed. The τ value represents the exponential component of the ex-Gaussian distribution that exists once the normal component (μ) has been removed. The overall ex-Gaussian distribution can therefore be considered as an algebraic addition of $\mu + \tau$ (Heathcote et al., 1991). These analyses have shown that the τ value, theoretically indicative of the prevalence of abnormally long response times (or attentional lapses) has a large effect on the shape of a response time distribution and therefore contributes substantially to the standard deviation of a response time dataset (Hervey et al., 2006).

There are many parallels that can be drawn between the deficits observed in ADHD populations and those seen in chronic cocaine studies. A review by Castellanos and Tannock (2002) cited both increased impacts of delay on reward-related behavior and deficits in working memory in ADHD populations. These results been observed in our laboratory in rhesus macaque monkeys after chronic cocaine self-administration as well as in human cocaine users by other laboratories (Hester and Garavan, 2008). Common brain areas, such as the ventrolateral prefrontal cortex, anterior cingulate, and "default-mode" circuitry have also been implicated in deficits in both ADHD populations and chronic cocaine users (Rubia et al., 2009; Clare Kelly et al., 2008; Liu et al., 2007).

To our knowledge, there is no published work detailing intra-individual/ex-Gaussian response time analysis after chronic cocaine use in either humans or non-human primates. The goal of this study was to examine response variability and the prevalence of attentional lapses after chronic cocaine self-administration in a cohort of rhesus macaque monkeys. Performing such a study in the primate model is unique and also advantageous due to the absence of

confounds such as poly-drug exposure, inconsistent dosage, and preexisting traits that confound studies in human cocaine addicts.

2.0 METHODS AND MATERIALS

The present study used 14(8 cocaine animals and 6 controls) adult male Rhesus macaque monkeys with no previous drug exposure other than as necessary for routine veterinary purposes. For all behavioral procedures including cognitive testing and cocaine self-administration, animals were restrained in primate chairs (Primate Products, Redwood City, CA) using standard pole-and-collar methods. All animals in this study had a vascular access port placed mid-scapula from which a catheter extended subcutaneously to an internal jugular vein (Bradberry et al. 2000). All procedures were in accord with the NIH Guide for the Care and Use of Laboratory Animals and the Institutional Care and Use Committee at the University of Pittsburgh(NIH publication no 86-23, revised 1987).

2.1 TOUCH SCREEN FAMILIARIZATION AND WATER REGUALATION

After an initial training period where water rewards were given for touching paper stimuli, the animals performed a series of tasks of gradually increasing difficulty (large, stationary stimuli to smaller, randomly placed stimuli) on 15” touch screen computer monitors. For each of these tasks, reward contingencies were set so that touch-screen interaction provided at least 50% of an animal’s daily water requirement; animals were also required to meet certain performance criteria before progressing to the next task in the familiarization sequence. The monitors used for these tasks (Elo systems CarollTouch) utilized infrared sensor grids to record touches, and were mounted in sound-attenuating chambers (Eckel Industries, Ontario, Canada model AB4240) fitted with 40W houselights. The E-prime software package (Psychology Software Tools, Pittsburgh, PA) was employed for all tasks in this study (training, Response-Time task, and Self-Administration) and was programmed to play white noise (approx. 60 dB) during cognitive testing.

Animals performed tasks for water rewards 5 days per week (Monday through Friday) with ad lib water over the weekend. On Tuesday through Friday afternoons, animals were supplemented with water to maintain adequate physiological needs (25 mL/kg/day).

2.2 COCAINE AND WATER SELF-ADMINISTRATION

Both cocaine and water self-administration took place 4 days per week (Tuesday through Friday). As previously stated, the self-administration procedures used the same chamber setup as the cognitive testing. The visual presentation of the administration program was identical for both cocaine and control groups, however there were differences in total administrations, inter-infusion interval, and touches to reward. Briefly, animals were presented with a stimulus (not used in any other task) and were required to repeatedly touch the stimulus until a reward was administered. After a reward was administered, there was an inter-infusion interval set so that control and cocaine animals spent approximately the same amount of time on the self-administration program.

For the cocaine group (n=8), animals were trained to self-administer cocaine in stages progressing according to the schedule in Table 1. The reason for the gradual increase in unit dose was to avoid any aversion due to the lack of familiarity with the drug experience.

Unit Dose	Fixed Ratio	Inter-infusion Interval (minutes)	# of Sessions
0.1 mg/kg	3	5	3
0.2 mg/kg	3	5	5
0.35 mg/kg	8	5	3
0.35 mg/kg	10	5	4
0.5 mg/kg	15	10	4
0.5 mg/kg	20	10	

Table 2.1. Cocaine infusions were administered as injections of cocaine solution directly into the implanted vascular access port of each animal. All infusions were automatically administered by the E-Prime self-administration program using parallel port output to syringe pumps (MED Associates, Georgia, Vermont).

Animals in the control group (n=6) were taught to self-administer water using the schedule in Table 2. Variables such as water amount, inter-infusion interval, and fixed ratio were adjusted so that animals would complete the administration program while having a similar number of total screen touches and program duration to the cocaine group.

H_2O per infusion	# of Infusions	Fixed Ratio	Inter-infusion Interval (minutes)	# of Sessions
1 mL/kg	6	3	5	2
1 mL/kg	6	3	2.5	4
1 mL/kg	6	5	2.5	2
1 mL/kg	6	8	3.3	3
1 mL/kg	6	10	3.3	8
0.33 mL/kg	18	10	3.3	4
0.66 mL/kg	18	10	3.3	

Table 2.2. Water infusions were administered through sipper tubes mounted to the primate chairs. All infusions were automatically administered by the E-Prime self-administration program using parallel port output to gravity fed liquid reward dispensers mounted above the testing chambers (Crist Instrument Co., Hagerstown, Maryland).

2.3 RESPONSE TIME TASK

The task used in this study was a simple stimulus response program in which animals were rewarded with water (through a sipper tube) for touching a single stimulus when it appeared on the screen. In each of the 50 trials per task session, a square stimulus of random size ranging from 0.5” to 1.0” on each side was presented in a random position on the touch-screen monitor. Correct responses resulted in a water reward of 0.15 mL/kg; there was no reward for incorrect responses. After each response (either correct or incorrect), there was a 2-second inter-trial interval before the start of the next trial. There was no limit set for how long an animal could

take to respond on a particular trial, however all responses longer than 5s were excluded in this study due to a presumed lack of engagement in the task.

Cocaine and control groups differed in their daily schedule in terms of when the response time task was administered in relation to the daily self-administration session. To avoid introducing any confounds due to acute drug effects on task performance, the cocaine group received the response time task prior to the self-administration session. The control group, that also received water rewards self-administration sessions, received the response time task after the water self-administration was completed. This schedule was adopted to ensure that animals would not receive a quantity of water during the response time task that would interfere with their engagement in the water self-administration task. For long term equivalency between the control and experimental groups, it was important that animals in both groups engage in equivalent amount of responses on the touch screen task used to self-administer either water or cocaine. This arrangement served as a conservative control, because the net effect predicted would be that the cocaine group would be more motivated for the water reward since they had not received any water yet that day, while the control group would be less motivated because they had just engaged in the self-administration task. A figure of RT task accuracy is presented in the results section to illustrate that the control group remained actively engaged in the RT task even after receiving water during self-administration.

The baseline pre-(water or cocaine) self-administration response task sessions for all animals were given after animals had already performed a delayed match-to-sample working memory task. This schedule was in place so that performance on the more challenging working memory task was not affected by water acquired during response task performance. As indicated by Figure 7, animals achieved accuracy averages of 65% or above and were therefore sufficiently engaged in the task.

2.4 DATA ANALYSIS

For all analyses in the present study, 10 RT task sessions from immediately before the self-administration period began were compared to the first 25 sessions of the task during the self-administration period. The first session analyzed occurred 24 hours after the first administration of cocaine, and all other sessions occurred 24 hours post-administration. Response times were defined as the time interval from stimulus presentation to screen touch.

For all statistical analyses, task response times were excluded if they were either <200 ms or >5000 ms. The presumption was that the short RTs indicated anticipatory responses rather than a response to stimulus presentation, and the long RTs indicated a lack of engagement. One-way ANOVAs were performed to compare means of 10 pre-administration sessions with 25 post-administration sessions (SigmaStat version 3.5, Systat Software). Values for one session of one cocaine group animal were excluded due to abnormally poor session performance, being defined as sessions with a mean response time greater than 2 standard deviations from the subject's mean for all other sessions. All tests were 2 sided with an alpha level = 0.05.

Calculation of all ex-Gaussian parameters was performed using MATLAB software (The Mathworks) and was based on procedures proposed by Lacouture and Cousineau, 2008. Briefly, this method of ex-Gaussian probability distrubution fitting uses the Fminsearch function of MATLAB to determine the ex-Gaussian parameters of maximum likelihood. This method employs the MATLAB Simplex search algorithm to search for the best fitting probability density function for a particular distribution dataset. To avoid potential search errors (such as local minima producing erroneous search parameters), starting point estimates were first calculate to narrow the search field. Much of this procedure is detailed in Lacouture and Cousineau, 2008, but procedural changes were made for input and output specific to our task data.

3.0 RESULTS

3.1 STANDARD MEASURES OF MEAN AND STANDARD DEVIATION

Although there appeared to be a slight increase in cocaine group mean response time following self-administration when compared to group pre-administration values, a one-way ANOVA on subject means revealed that this difference was not significant (pre-admin mean: 629±45, post-admin mean: 864±135, F=3.4, p=0.09). No difference was observed in control group mean response time between pre-administration and post-administration sessions (pre-admin mean: 572±31, post-admin mean: 667±57). No difference was observed between cocaine and control groups prior to self-administration.

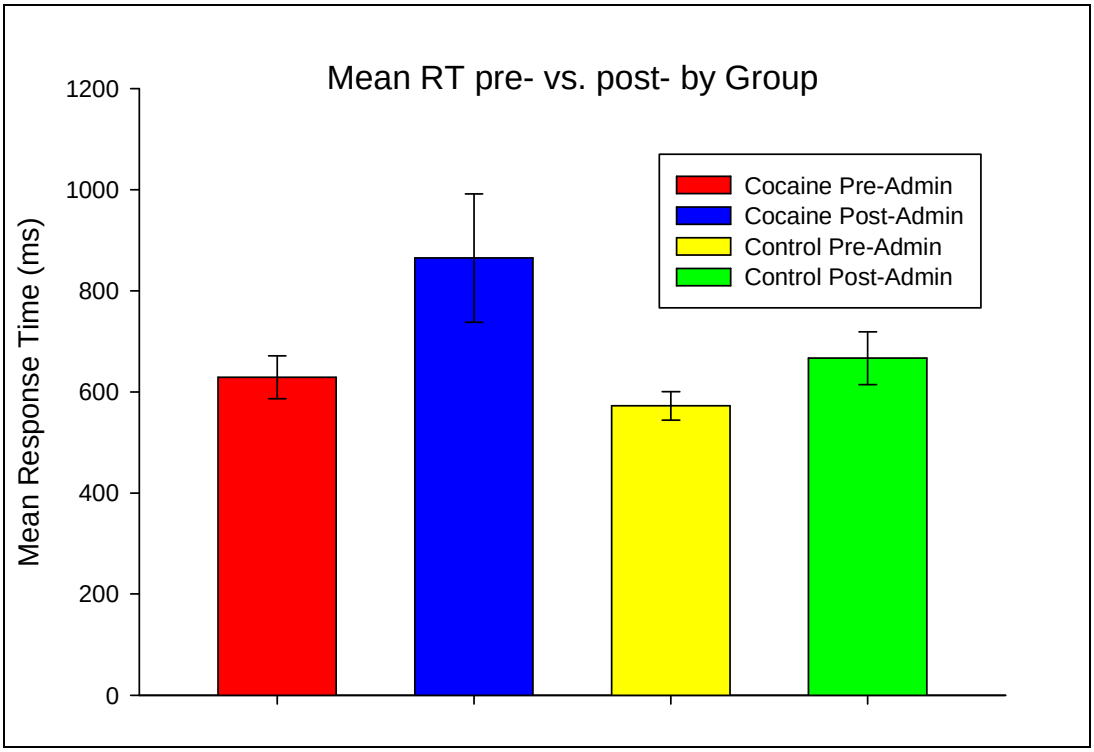

Figure 3.1. Neither group showed a significant change in mean response time following self-administration.

Analysis of pre- and post-administration response time standard deviation revealed that the cocaine group exhibited significantly greater response time standard deviation during the drug administration period (pre-admin SD: 448 ±56, post-admin SD: 716±120, $F=4.7$, $p<0.05$), whereas no differences were observed in the control group (pre-admin SD: 384±55, post-admin SD: 487±86). No difference was observed between cocaine and control groups prior to self-administration.

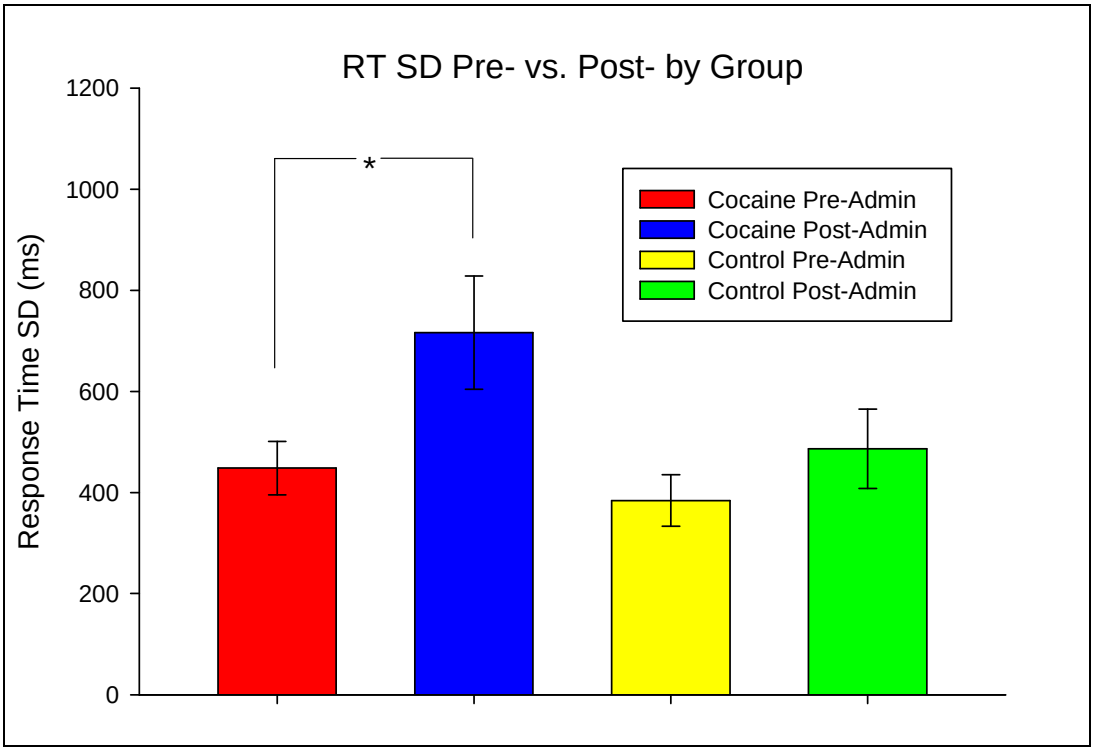

Figure 3.2. Cocaine group displayed increased response time standard deviation following chronic cocaine self-administration

3.2 EX-GAUSSIAN PARAMETERS OF INTRA-INDIVIDUAL RESPONSE TIME

Analyses were performed to extract individual animal ex-Gaussian parameters for both mu and tau to further examine the differences in response time variability that were observed.

The calculated μ, or Gaussian mean, values showed that individual animals in the cocaine group did not significantly differ from pre- to post-administration. Interestingly, there was somewhat of a decrease in cocaine group mean μ values after cocaine self-administration, however a one-way ANOVA on subject means revealed that this difference was not significant (pre-admin μ: 299±31, post-admin μ: 234±23, $p=0.09$). No difference was observed in the control group (pre-admin μ: 272±48, post-admin μ: 330±9). There was no difference observed between cocaine and control groups prior to self-administration.

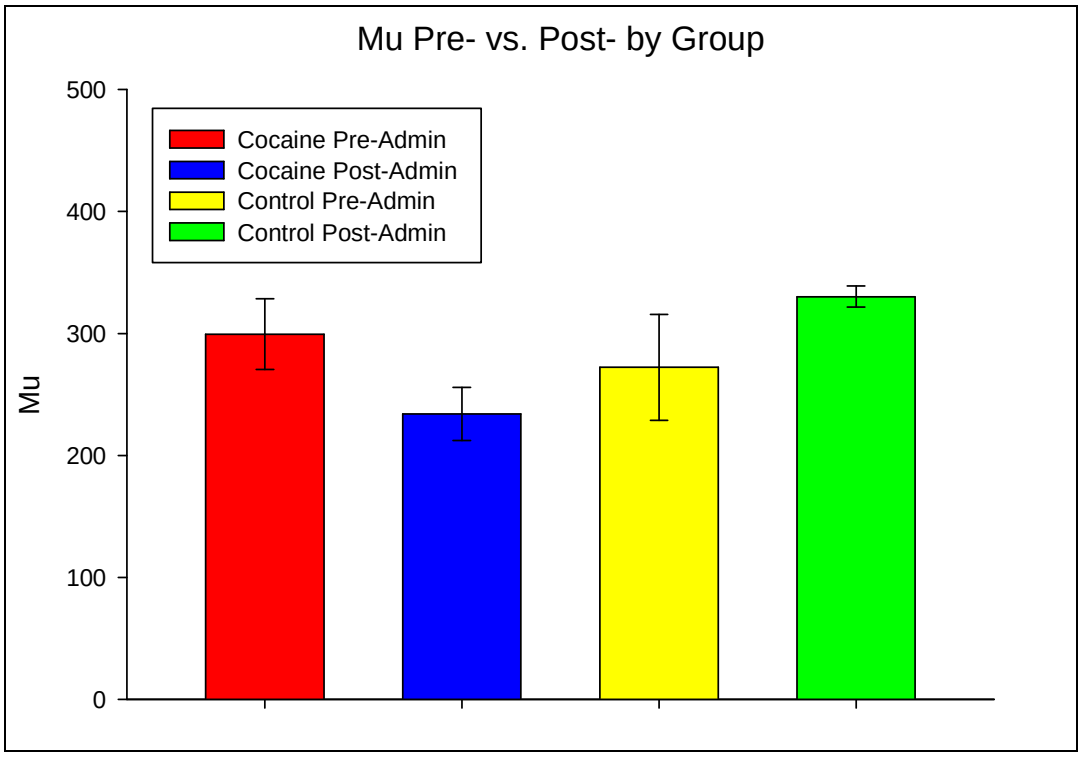

Figure 3.3. Neither the cocaine nor the control group showed any significant difference in the extracted normal mean value (mu) of response time distributions after the onset of cocaine self-administration

The value of τ, or the exponential value indicative of the contribution of the right-tail of the RT distribution, showed a significant increase in the cocaine group after chronic drug self-administration (pre-admin τ: 339 ±49, post-admin τ: 633±135, $F=4.8$, $p<0.05$). No difference was observed in the control group (pre-admin τ: 289 ±42, post-admin τ: 312±55). There was no difference observed between cocaine and control groups prior to self-administration.

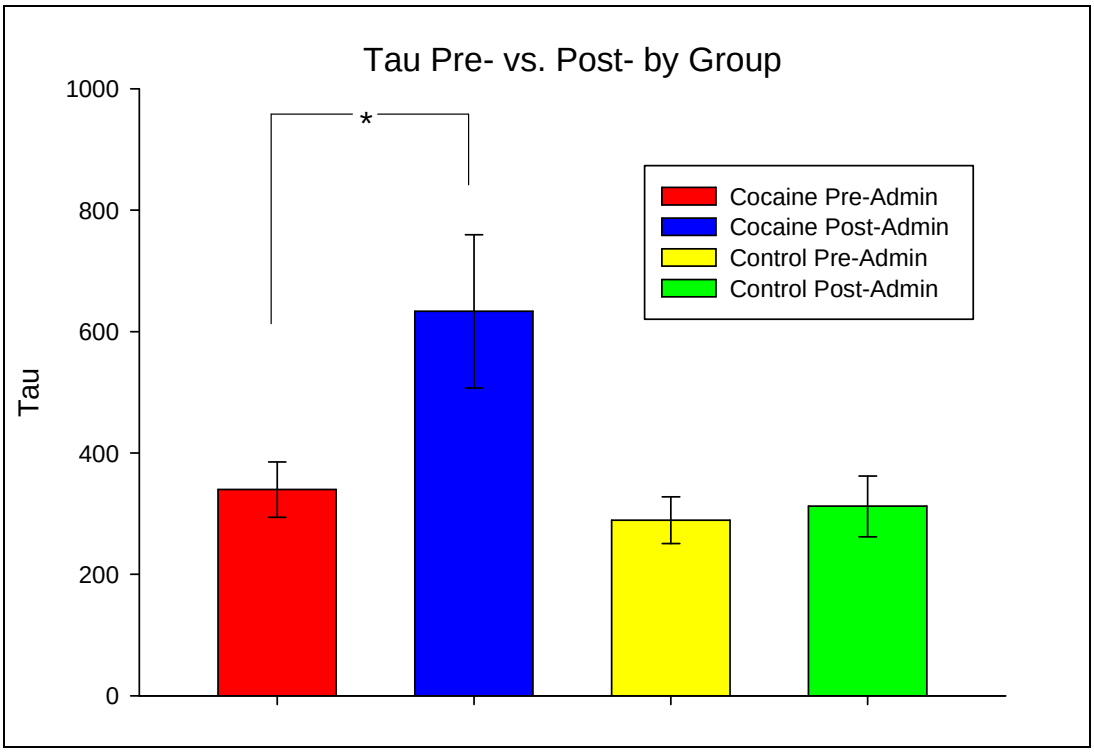

Figure 3.4. The cocaine group showed a significant increase in tau values after the onset of drug administration, indicating a greater skew in animal response time distributions.

To provide a general summary of the results observed, figures 3.5 and 3.6 show histograms and distribution curves for pooled data of all responses. Figure 5 shows histograms of all group responses both pre- and post-administration and the ex-gaussian probability distributions that were created using these data. One noticeable aspect of the cocaine post-administration figure is the increased number of responses along the entire 5000 ms axis, thus creating the elongated tail that can be seen in the ex-Gaussian probability curve. For a more direct pre-/post- visual comparison (without the effects of different numbers of sessions) probability density ex-Gaussian distributions are plotted in figure 3.6. The control plots are very similar, while the elongated tail (increased τ) and shorter peak probability response time (decreased μ) can be seen in the cocaine group plots.

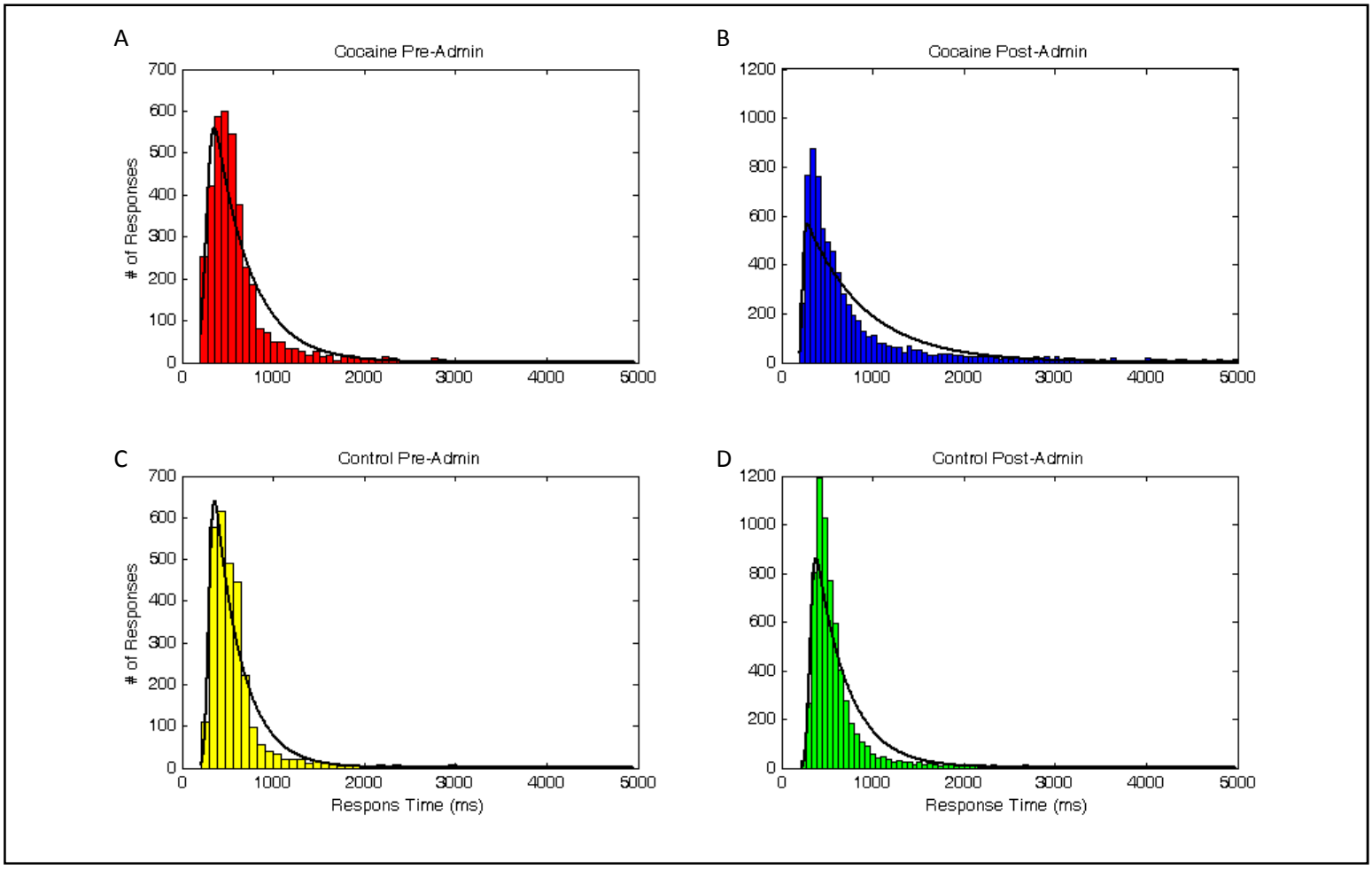

Figure 3.5. Histograms of all responses both pre-administration (A,C) and post-administration (B,D). Panel B shows the increased skew and number of abnormally slow responses following cocaine self-administration

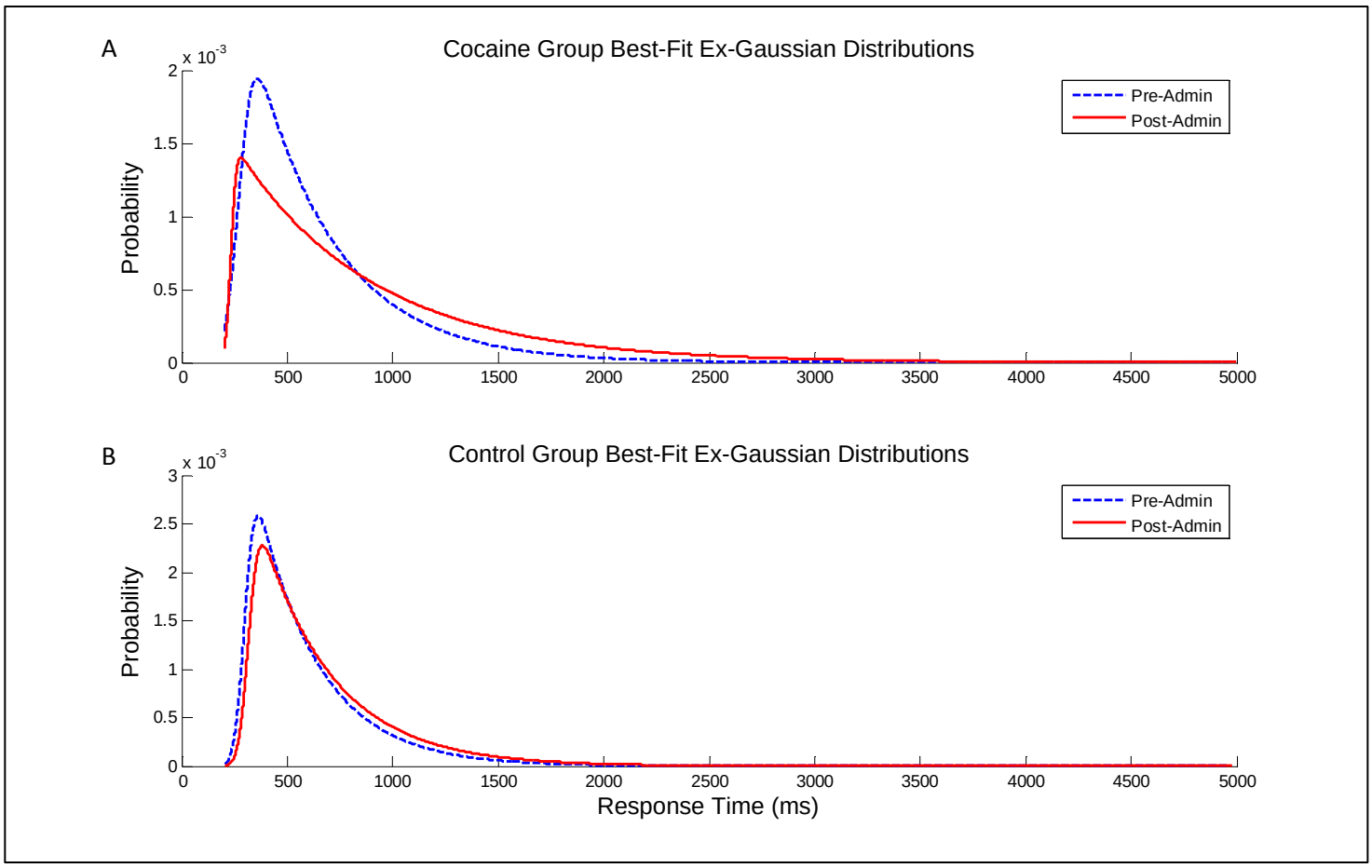

Figure 3.6. Best-fit ex-Gaussian response time distributions for both cocaine and control groups, pre- and post-administration. Panel A shows the change distribution shape after chronic cocaine self-administration.

Accuracy values were calculated to illustrate that, although the control group received daily water prior to performing the RT task, the group suffered from no lack of motivation as no difference was observed in accuracy from pre-administration to post-administration sessions (pre-admin accuracy: 0.70 ±0.05, post-admin accuracy: 0.66±0.07). The cocaine group did show a significant decrease in accuracy following cocaine self-administration (pre-admin accuracy: 0.69 ±0.06, post-admin accuracy: 0.48±0.08, $F=4.9$, $p<0.05$). No difference was observed between cocaine and control groups prior to self-administration.

3.3 OTHER ANALYSES

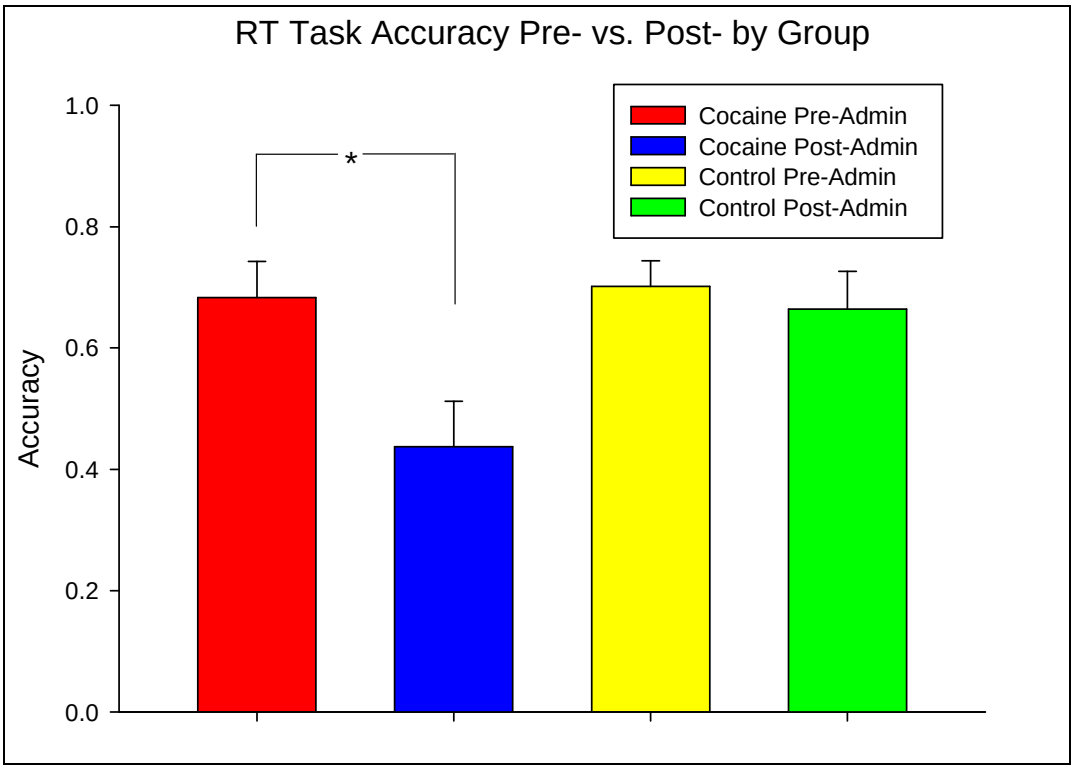

Figure 3.7. Only the cocaine group, whose daily water came solely from the RT task, showed a decrease in accuracy following self-administration

An analysis of correct only responses shows an increased tau in cocaine animals after self-administration, but this increase is not significant (pre-admin τ: 281 ±38, post-admin τ: 400±74, $p<0.17$). This measure may not be representative because of the small number of correct touches for cocaine animals, and future analysis of a greater number of sessions will be more definitive. This result does suggest that animals respond correctly after a large number of attentional lapses, and furthermore confirms that these lapses are not due to poor motivation, otherwise a smaller proportion of attentional lapses would occur prior to correct responses. No difference was observed in the control group.

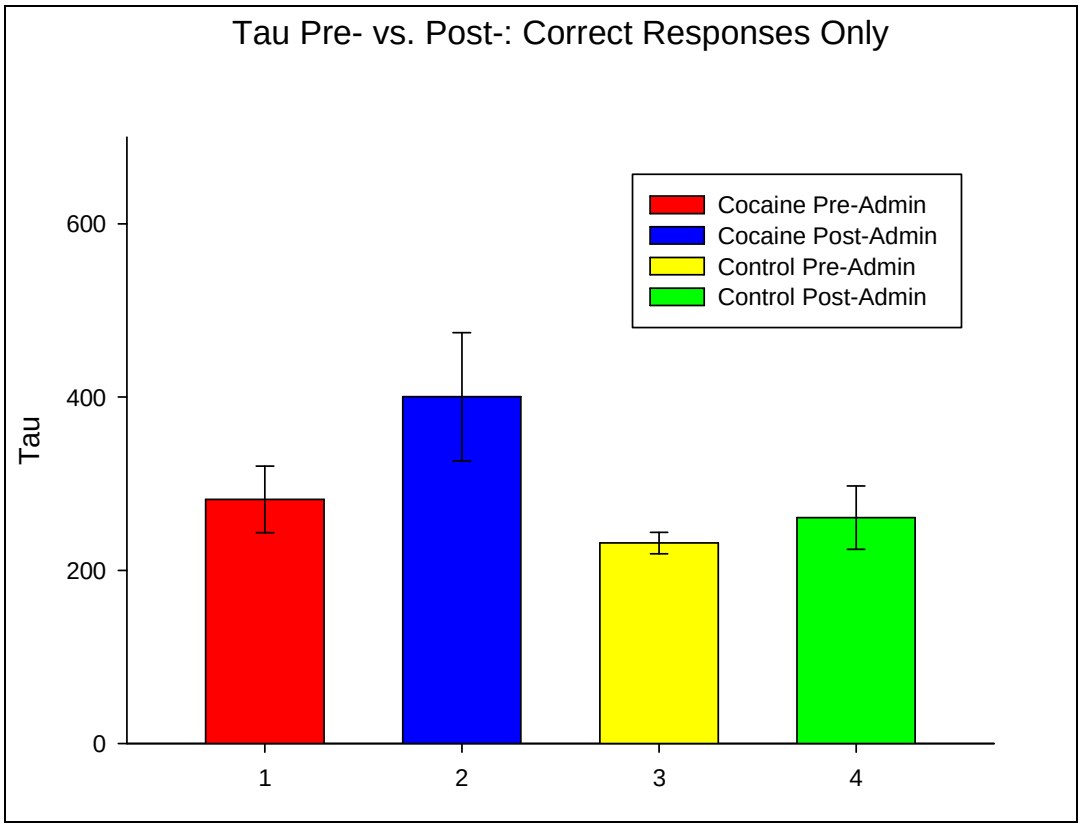

Figure 3.8. Tau values calculated for correct trials only in both treatment groups, pre- and post-administration.

Another area of interest in this study was to determine if subjects displayed any variability increase in spatial responding, in addition to the increased temporal response time variability previously discussed. Although animals did show a decrease in accuracy following cocaine self-administration, there is no evidence of any motivational deficits (no change in overall response time, and potentially faster response times in the absence of attentional lapses). Any observed increases in miss distance therefore may be related to disruptions in sensorimotor processing as a result of chronic cocaine exposure. Analysis of miss distance showed a nonsignificant increase in the cocaine post-administration group (pre-admin distance: 126 ±25, post-admin distance: 183±22, $p<0.09$). No difference was observed in the control group.

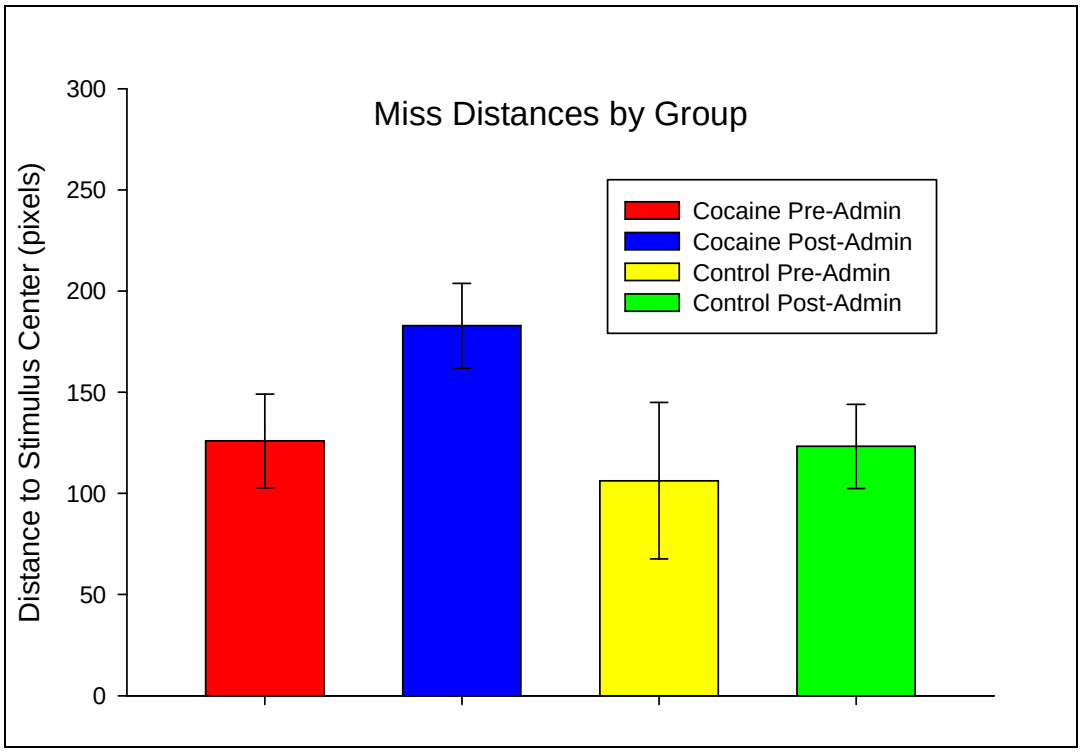

Figure 3.9. Analysis of mean distance to stimulus center on incorrect trials in all groups. The cocaine post-administration shows a nonsignificant increase in miss distances despite having no indication of any motivational deficits.

4.0 DISCUSSION

The goals of this study were to determine, using a simple response time task, if rhesus macaque monkeys showed increases in intra-subject variability after chronic cocaine self-administration. Additionally, we sought to determine if any potential change in response variability could be attributed to a particular ex-Gaussian component of the distribution. The main findings that emerged from this analysis were: (1) animals became more variable in their responding after chronic cocaine self-administration; (2) animals exhibited a greater number of abnormally long response times after chronic cocaine self-administration. In all analyses performed during this study, a control group of n=6 that self-administered water served to show that the observed results were not a result of the self-administration procedure by itself.

The finding that cocaine exposure resulted in an increase in overall response time variability was significant for several reasons. One clear advantage of the primate model compared with clinical studies is that drug intake can be monitored extremely closely. For all of the post-administration sessions in this study, approximately 24 hours had elapsed since the last cocaine administration, eliminating the possibility that acute drug effects had an influence on the observed response time variability. This finding also suggests cocaine use may have consequences in common with clinical disorders such as ADHD and autism where increased response variability has been illustrated (Johnson et al., 2007; Di Martino et al., 2008).

Ex-Gaussian analysis of response time distributions revealed that animals exhibited a significantly higher number of abnormally long response times after exposure to cocaine. The significantly higher value of τ indicates that response time distributions of the cocaine group were much more skewed after the self-administration procedure began. The impact of this skew can be appreciated in the context of both standard mean response time and the normal mean. Upon examination of mean response time, it appears that animals respond more slowly after exposure to cocaine. The calculation of μ indicates that, while not attaining statistical significance, the Gaussian mean response time decreased after cocaine exposure. Taken together, these findings illustrate the large impact that intermittent abnormally long response times have on a subject's overall response time distribution, and that these responses likely account for the finding of increased overall variability after cocaine exposure.

Increased τ values, although theoretical in their conceptualization, are often considered to represent attentional lapses that result in more positively skewed response time distributions (Leth-Steensen et al., 2000). While cocaine use has long been associated with deficits in tasks such as those involving discrimination learning (Jentsch et al., 2002; Liu et al., 2007), attentional testing has thus far been inconsistent in task structure and may suffer from the potential confounds of clinical testing (Jovanovski et al., 2005; Colzato et al., 2009). Our finding of increased lapses in attention after cocaine exposure brings into context a variety of recent imaging literature that examines these lapses in human subjects.

Imaging studies of attentional lapses in both clinical populations and healthy subjects have implicated brain regions such as the prefrontal cortex, cingulate, and regions of the temporal lobe (Clare Kelly et al., 2008; Weissman et al., 2006). While the activity changes in these areas that are responsible for attentional lapses are still debatable, evidence from our laboratory and others have indicated cocaine-related deficits on tasks thought to involve the same or related circuitry (Li et al., 2006;Beveridge et al., 2006; Liu et al., 2007, Goldstein et al., 2007). Given that disorders characterized by attention deficits are thought to involve the same neurotransmitter systems that are affected by cocaine exposure, the present study supports the notion that there may be some similar cognitive impairment involved in these two conditions.

In terms of the neurotransmitter systems involved in ADHD and cocaine addiction, there are both similarities and differences. ADHD has been thought of as a condition that almost exclusively involves dopaminergic neurotransmission. This hypothesis has been recently supported by human PET studies that found reduced striatal dopamine but not serotonin reuptake (Hesse et al., 2009). Cocaine exposure is also thought to exert its reinforcing effects by blocking dopamine reuptake (Volkow et al., 1997; Nader et al., 2002), but also binds to both serotonin and norepinephrine reuptake transporters (Bennett et al., 1995). Both the discriminative stimulus effects of cocaine and stress-induced reinstatement have been significantly altered by specific pharmacological manipulations norepinephrine transmission (Spealman, 1995; Platt et al., 2007; Kleven and Koek, 1998). It is unclear which transmitter system is responsible for the deficits in attention that have been observed in chronic cocaine users, and further studies are required to determine if ADHD and cocaine abuse alter the attention system through common mechanisms.

In discussing some potential mechanisms for the attentional deficits observed in this study, the temporal relationship of testing and self-administration is important. In this particular model of cognitive testing, all measure of performance were acquired 24 hours after cocaine self-administration. In such a testing regime, it is possible that subjects are experiencing the same low levels of norepinephrine and dopamine that are though to cause attentional lapses in ADHD populations. After just 5 days of cocaine administration, increased trafficking of norepinephrine transporters has been observed, presumably due to increased autoreceptor activation (Beveridge et al., 2005). If the subjects in our study are experiencing increased trafficking of reuptake transporters, it is possible that they are experiencing below baseline monoamine transmission 24

hours after cocaine administration. Although through a different mechanism, this scenario would produce ADHD-like neurotransmission 24 hours after the last administration of cocaine under chronic conditions.

Another potential mechanism deals with the growing field of research involving the so-called "default mode network" that is actively suppressed during task performance. Several studies have found that inability to suppress the default mode network or dysregulation of the network with its antiphase "task positive" regions result in attentional lapses and response variability (Weissman et al., 2006; Kelly et al., 2008). These studies suggest that dysregulation of brain activity and/or transmitter systems may have a greater impact on attention than directional shifts. A more recent study, however, has found that decreased dopamine specifically leads to attentional lapses by interrupting the suppression of the default mode network during tasks involving visuospatial attention (Tomasi et al., 2009). This is in agreement with the timeline mentioned above in that chronic cocaine users are experiencing decreased neurotransmission (through reuptake transporter upregulation) 24 hours after cocaine administration.

4.1 FUTURE DIRECTIONS

The present study found significant effects of chronic cocaine use on response variability and attention despite using relatively simple cognitive test. Observing such results in a stimulus-response task has illustrated the robust deficits associated with chronic cocaine use. We have also determined that the impairments in attention associated with cocaine are not due to acute drug effects or preexisting conditions. Among the potential future directions of the laboratory are to continue examining the impact of cocaine administration on attention after a longer self-administration period and perhaps with a more widely used sustained attention task. The laboratory currently uses procedures such as microdialysis and electrophysiological recording that will potentially be used to further investigate the neurobiology of attention deficits following chronic cocaine self-administration.

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